

## **M<sub>3</sub> MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS**

### **FIELD OF THE INVENTION**

This invention relates to novel bicyclic amine compounds, pharmaceutical compositions, processes for their preparation, and use thereof in treating M<sub>3</sub>

5 muscarinic acetylcholine receptor mediated diseases.

### **BACKGROUND OF THE INVENTION**

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors – the nicotinic and the  
10 muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M<sub>1</sub>-M<sub>5</sub>, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely  
15 distributed in vertebrate organs, and these receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, bladder and gastrointestinal tract, M<sub>3</sub> mAChRs mediate contractile responses (1989. The Muscarinic Receptors. The Humana Press, Inc., Clifton, NJ).

Muscarinic acetylcholine receptor dysfunction has been noted in a variety of  
20 different pathophysiological states. For instance, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M<sub>2</sub> muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation. This mAChR dysfunction results in airway  
25 hyperreactivity mediated by increased stimulation of M<sub>3</sub> mAChRs. Similarly, inflammation of the gastrointestinal tract in inflammatory bowel disease (IBD) results in M<sub>3</sub> mAChR-mediated hypermotility (Oprins, J. C. J., HP. Meijer, and J. A. Groot. 2000. Tumor Necrosis Factor- $\alpha$  Potentiates Ion Secretion Induced by Muscarinic Receptor Activation in the Human Intestinal Epithelial Cell Line HT29cl.19A. Ann NY Acad Sci 915:102-106). Incontinence due to bladder  
30 hypercontractility has also been demonstrated to be mediated through increased stimulation of M<sub>3</sub> mAChRs. Thus the identification of subtype-selective mAChR antagonists may be useful as therapeutics in these mAChR-mediated diseases.

Despite the large body of evidence supporting the use of anti-muscarinic  
35 receptor therapy for treatment of a variety of disease states, relatively few anti-

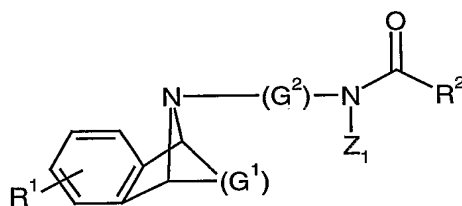
muscarinic compounds are in use in the clinic. Thus, there remains a need for novel compounds that are capable of causing blockade at M<sub>3</sub> mAChRs. Conditions associated with an increase in stimulation of M<sub>3</sub> mAChRs, such as asthma, COPD, IBD and urinary incontinence would benefit by compounds that are inhibitors of  
 5 mAChR binding.

### **SUMMARY OF THE INVENTION**

This invention provides for a method of treating a muscarinic acetylcholine receptor (mAChR) mediated disease, wherein acetylcholine binds to an M<sub>3</sub> mAChR  
 10 and which method comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof which comprises administering to aforementioned mammal an effective amount of a compound of  
 15 Formula (I).

The present invention also provides for the novel compounds of Formula (I), and pharmaceutical compositions comprising a compound of Formula (I), and a pharmaceutical carrier or diluent:



**Formula (I)**

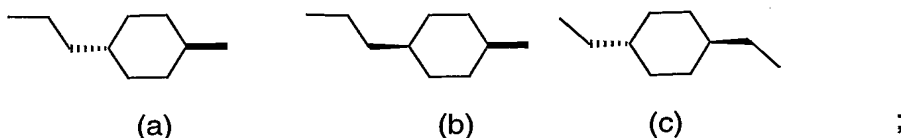
wherein:

Z<sub>1</sub> is, independently, H or C<sub>1-6</sub> alkyl;

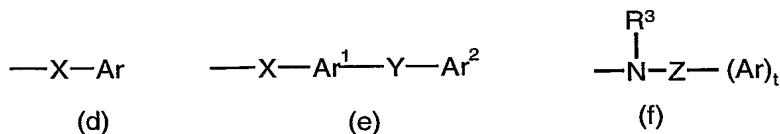
R<sup>1</sup> is, independently, a substituent selected from the group consisting of:  
 25 Hydrogen, halogen, C<sub>1-4</sub> alkyl, -C(O)(C<sub>1-6</sub> alkyl), -CO<sub>2</sub>(C<sub>1-6</sub> alkyl), -C(O)(aryl) and -C(O)[(C<sub>1-6</sub> alkyl)-aryl];

G<sup>1</sup> is, independently, CH<sub>2</sub>-CH<sub>2</sub> or CH=CH;

G<sup>2</sup> is, independently, C<sub>4-7</sub>alkyl or a group of the formula (a), (b) or (c):



$R^2$  is, independently, a group of the formula (d) or (e):



5

wherein

X is, independently, a bond,  $NR^3$  or  $C_{1-4}$  alkyl;

10  $R^3$  is, independently, selected from the group consisting of H, optionally substituted  $C_{1-6}$  alkyl and  $C_{1-4}$  alkyl-aryl;

Z is, independently, optionally substituted  $C_{1-6}$  alkyl, and  $C_{1-6}$  alkyl- $Y^2$ ; or Z and  $R^3$  or Z and Ar may come together to form a 4-7 membered ring;

15 Ar is selected from the group consisting of an optionally substituted phenyl ring, an optionally substituted 5- or 6- membered aromatic heterocyclic ring; an optionally substituted bicyclic or heterobicyclic ring system; and an optionally substituted tricyclic or heterotricyclic ring system;

$Ar^1$  and  $Ar^2$ , are each, independently, selected from the group consisting of an optionally substituted phenyl ring and an optionally substituted 5- or 6- membered aromatic heterocyclic ring;

20 Y is, independently, selected from the group consisting of a bond,  $-NHCO-$ ,  $-CONH-$ ,  $-CH_2-$ , and  $-(CH_2)_mY^1(CH_2)_n$ -wherein  $Y^1$  represents O, S,  $SO_2$ , or CO and m and n each represent zero or 1 such that the sum of m+n is zero and 1; provided that when  $R^2$  represents a group of formula (d) wherein X is a bond, any substituent present in Ar *ortho* to the carboxamide moiety is necessarily a hydrogen or a methoxy group

$Y^2$  is, independently, selected from the group consisting of  $NR^3$ , O, S,  $-NHC(O)-$ , and  $-C(O)NH-$ ;

t is, independently, selected from the group consisting of an integer between 0 and 3.

When  $R^1$  represents an aroyl, or aroyl- $C_{1-4}$ alkyl, , the aryl moiety may be selected from an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered heterocyclic ring. In the group  $R^1$  an aryl moiety may be optionally substituted by one or more substituents selected from hydrogen, halogen, amino, cyano,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkylamino,  $C_{1-4}$ dialkylamino,  $C_{1-4}$ alkylamido,  $C_{1-4}$ alkanoyl, or  $R^5R^6NCO$  where each of  $R^5$  and  $R^6$  independently represents a hydrogen atom or  $C_{1-4}$ alkyl group.

A halogen atom present in the compounds of formula (I) may be fluorine, chlorine, bromine or iodine.

An optionally substituted 5- or 6-membered heterocyclic aromatic ring, as defined for any of the groups Ar,  $Ar^1$  or  $Ar^2$  may contain from 1 to 4 heteroatoms selected from O, N or S. When the ring contains 2-4 heteroatoms, one is preferably selected from O, N and S and the remaining heteroatoms are preferably N. Examples of 5 and 6-membered heterocyclic groups include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl, pyrazolyl, isothiazolyl, and isoxazolyl.

Examples of bicyclic, for example bicyclic aromatic or heteroaromatic, ring systems for Ar include naphthyl, indazolyl, indolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzisothiazolyl, quinolinyl, quinoxolinyl, quinazolinyl, cinnolinyl, isoquinolinyl, pyrazolo[1,5-a]pyrimidyl, pyrrolo[3,2-b]pyridyl, pyrrolo[3,2-c]pyridyl, thieno[3,2-b]thiophenyl, 1,2-dihydro-2-oxo-quinolinyl, 3,4-dihydro-3-oxo-2*H*-benzoxazinyl, 1,2-dihydro-2-oxo-3*H*-indolyl.

The rings Ar,  $Ar^1$ , or  $Ar^2$  may each independently be substituted optionally by one or more substituents selected from: a hydrogen or halogen atom, or a hydroxy, oxo, cyano, nitro, trifluoromethyl,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkylenedioxy,  $C_{1-4}$ alkanoyl,  $C_{1-4}$ alkylsulfonyl,  $C_{1-4}$ alkylsulfinyl,  $C_{1-4}$ alkylthio,  $R^7SO_2N(R^8)-$ ,  $R^7R^8NSO_2-$ ,  $R^7R^8N-$ ,  $R^7R^8NCO-$ ,  $R^7OC(O)-$  or  $R^7CON(R^8)-$  group wherein each of  $R^7$  and  $R^8$  independently represents a hydrogen atom or a  $C_{1-4}$ alkyl group, or  $R^7R^8$  together form a  $C_{3-6}$  alkylene chain.

Alternatively, Ar and Ar<sup>2</sup> may be optionally substituted by one or more 5- or 6-membered heterocyclic rings, as defined above, optionally substituted by a C<sub>1-2</sub> alkyl or R<sup>7</sup>R<sup>8</sup>N- group; wherein R<sup>7</sup> and R<sup>8</sup> are as defined above.

In the rings Ar and Ar<sup>2</sup> substituents positioned *ortho* to one another may be  
5 linked to form a 5- or 6- membered ring.

It will be appreciated that for use in medicine the salts of formula (I) should be physiologically acceptable. Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or  
10 phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other non-physiologically acceptable salts eg. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates  
15 of compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The following terms, as used herein, refer to:

- 20 • "optionally substituted" – one or more substituents selected from: halo; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub> alkoxy, such as methoxy or ethoxy; S(O)<sub>m'</sub> C<sub>1-10</sub> alkyl, wherein m' is 0, 1 or 2, such as methyl thio, methyl sulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR<sub>4</sub>R<sub>5</sub> group; NHC(O)R<sub>4</sub>; C(O)NR<sub>4</sub>R<sub>5</sub>; C(O)OH; C(O)OR<sup>4</sup>S(O)<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>; NHS(O)<sub>2</sub>R<sub>20</sub>, C<sub>1-10</sub>  
25 alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted C<sub>1-10</sub> alkyl, such CF<sub>3</sub>;
- "halo" - all halogens, that is chloro, fluoro, bromo and iodo.
- "C<sub>1-10</sub>alkyl" or "alkyl" - both straight and branched chain moieties of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not  
30 limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- "cycloalkyl" is used herein to mean cyclic moiety, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.

• "alkenyl" is used herein at all occurrences to mean straight or branched chain moiety of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

5       • "aryl" - phenyl and naphthyl;

• "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, tetrazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.

• "heterocyclic" (on its own or in any combination, such as "heterocyclicalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, thiomorpholine, or imidazolidine. Furthermore, sulfur may be optionally oxidized to the sulfone or the sulfoxide.

• "aryalkyl" or "heteroaryalkyl" or "heterocyclicalkyl" is used herein to mean C<sub>1</sub>-10 alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as also defined herein, unless otherwise indicated.

Particular preferred compounds according to the invention include those specifically exemplified and named hereinafter:

2-Methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;

8-Chloro-2-methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide ;

8-Methyl-quinoline-5-carboxylic acid (4-{2-[6-butyryl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide ;

2-Methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-butyryl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide ;

2-Methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;

N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-1-(2-phenylethyl)-1-(phenylmethyl)urea;

- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2-hydroxy-2,2-diphenylethyl)urea;  
 N-[2-({[(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)amino]carbonyl}amino)ethyl]-4-methylbenzenesulfonamide;
- 5 1,1-dimethylethyl N-{{[(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)amino]carbonyl}-L-phenylalaninate;  
 N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-(3,3-diphenylpropyl)-N-methylurea;  
 3-[[{[(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)amino]carbonyl}amino)methyl]benzenesulfonamide formate;
- 10 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2-hydroxy-1,1-diphenylethyl)urea formate;  
 N,N'-bis(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)urea
- 15 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(3-hydroxy-3,3-diphenylpropyl)urea formate;  
 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[(1S)-2-hydroxy-1-methyl-2,2-diphenylethyl]urea formate;  
 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-
- 20 (cyclohexylmethyl)urea;  
 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[(2-hydroxyphenyl)methyl]urea;  
 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]urea;
- 25 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[(4-fluorophenyl)methyl]urea;  
 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[(4-fluorophenyl)methyl]urea;  
 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-
- 30 (2,3-dihydro-1H-inden-1-yl)urea;  
 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(3-phenylpropyl)urea;  
 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[(4-chlorophenyl)methyl]urea;

- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1,1a,6,6a-tetrahydrocyclopropa[a]inden-1-yl)urea;  
 N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-(3-hydroxypropyl)-N-(phenylmethyl)urea;
- 5 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-{[4-(trifluoromethyl)phenyl]methyl}urea;  
 1,1-dimethylethyl 2-[[[(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)amino]carbonyl}benzoate;  
 N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-
- 10 2,2-diphenylpropanamide;  
 N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-4-[(phenylcarbonyl)amino]benzamide;  
 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2,2-diphenylethyl)urea;
- 15 N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N,1-bis(phenylmethyl)urea;  
 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(3,3-diphenylpropyl)urea;  
 1-Benzyl-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-
- 20 cyclohexyl}-urea  
 1-(1-Naphthalen-1-yl-ethyl)-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea.

- Preferred compounds according to the invention include those specifically
- 25 exemplified and named hereinafter:  
 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2-(4-pyridinyl)acetamide;  
 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2-pyridinylmethyl)urea;
- 30 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(4-hydroxycyclohexyl)urea;  
 N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-methyl-N-(phenylmethyl)urea;  
 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-
- 35 [2-(2-pyridinyl)ethyl]urea;



- N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2-(2-pyrimidinylthio)acetamide;
- N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-quinolinecarboxamide;
- 5 N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-1-methyl-1H-indole-2-carboxamide;
- (2E)-N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-4-oxo-4-phenyl-2-butenamide;
- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-
- 10 (1H-indol-3-ylmethyl)urea;
- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1H-benzimidazol-2-ylmethyl)urea;
- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1,2,3,4-tetrahydro-2-naphthalenyl)urea;
- 15 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1,2,3,4-tetrahydro-1-naphthalenyl)urea;
- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N,N-dimethylphenylalaninamide;
- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-
- 20 (4-phenylbutyl)urea;
- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2-methyl-1,2,3,4-tetrahydro-2-naphthalenyl)urea;
- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2-methyl-1,2,3,4-tetrahydro-2-naphthalenyl)urea;
- 25 N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-4-(2-pyridinyl)-1-piperazinecarboxamide;
- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[2-(4-pyridinyl)ethyl]urea formate;
- N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-
- 30 2,2-diphenylacetamide;
- N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2,2-diphenylacetamide;
- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[3-(1H-imidazol-1-yl)propyl]urea formate;

- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-  
{[4-(trifluoromethyl)phenyl]methyl}urea;  
N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-  
4-(phenylmethyl)-1-piperazinecarboxamide;
- 5 N-[5-[(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-  
cyclohexyl)amino]-5-oxopentyl]benzamide;  
1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-  
(1H-indol-3-ylmethyl)urea formate;  
1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-  
10 {[3-(dimethylamino)phenyl]methyl}urea formate;  
N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-  
3-(4-methylphenyl)-3-phenylpropanamide;  
N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-  
4,4-diphenylbutanamide;
- 15 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2-  
(methoxy)-2,2-diphenylacetamide;  
1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-  
(1-naphthalenylmethyl)urea formate;  
N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-  
20 4-(phenylmethyl)-1-piperazinecarboxamide formate;  
1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-  
(2-{3-[hydroxy(3-pyridinyl)methyl]phenyl}ethyl)urea;  
1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-  
[1-(phenylmethyl)-4-piperidinyl]urea formate;
- 25 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-  
(3-phenylpropyl)urea trifluoroacetate;  
1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-  
[5,8-bis(methoxy)-1,2,3,4-tetrahydro-2-naphthalenyl]urea formate;  
N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-  
30 N-(3,3-diphenylpropyl)-N-propylurea;  
1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-  
(3,3-diphenylpropyl)urea formate;  
1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-  
(1-methyl-2,2-diphenylethyl)urea formate;

- N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2-[(2-methylphenyl)(phenyl)methyl]benzamide;
- N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-4-(diethylamino)-2,2-diphenylbutanamide;
- 5 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2-{3-[hydroxy(3-pyridinyl)methyl]phenyl}ethyl)urea formate;
- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1,1-dimethyl-3,3-diphenylpropyl)urea formate;
- N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-10 N-(3,3-diphenylpropyl)-N-ethylurea formate;
- N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-methyl-N-(2,2,2-triphenylethyl)urea;
- N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-phenyl-3-{3-[(phenylmethyl)oxy]phenyl}propanamide;
- 15 N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2-hydroxy-2,2-diphenylacetamide trifluoroacetate ;
- N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-ethyl-N-(3-hydroxy-3,3-diphenylpropyl)urea formate;
- N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-20 2-{bis[4-(dimethylamino)phenyl]methyl}benzamide;
- N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[4-(dimethylamino)phenyl]-3-phenylpropanamide trifluoroacetate;
- N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-(3,3-diphenylpropyl)-N-(phenylmethyl)urea formate;
- 25 N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2,2-bis(4-chlorophenyl)acetamide trifluoroacetate;
- N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-4-(diethylamino)-2,2-diphenylbutanamide trifluoroacetate;
- 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-30 [3-(4-biphenyl)-3-(4-chlorophenyl)-3-hydroxypropyl]urea formate;
- 1-(4-Bromo-benzyl)-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea;
- 1-(1,1-Diphenyl-methyl)-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea;

- 1-(2-Methoxy-benzyl)-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea;
- 1-(3-Methoxy-benzyl)-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea;
- 5 1-(4-Methoxy-benzyl)-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea;
- 2-Methyl-quinoline-5-carboxylic acid {4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide;
- 8-Chloro-2-methyl-quinoline-5-carboxylic acid {4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide;
- 10 8-Methoxy-2-methyl-quinoline-5-carboxylic acid {4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide;
- Quinoxaline-5-carboxylic acid {4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide;
- 15 Quinoline-5-carboxylic acid {*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide;
- 8-Methyl-quinoline-5-carboxylic acid {*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide;
- 2-Methyl-quinoline-5-carboxylic acid {*trans*-4-[(1*S*,4*S*)-1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl) methyl]-cyclohexylmethyl}-amide;
- 20 8-Chloro-2-methyl-quinoline-5-carboxylic acid {*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide;
- 2,8-Dimethyl-quinoline-5-carboxylic acid {*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide;
- 25 1-((*S*)-1-Naphthalen-1-yl-ethyl)-3-{*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-urea;
- 1-((*R*)-1-Naphthalen-1-yl-ethyl)-3-{*trans*-4-[(1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl)-cyclohexylmethyl]-urea;
- Isoquinoline-1-carboxylic acid {*trans*-4-[(1*S*,4*R*)-2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide;
- 30 Acridine-9-carboxylic acid {*trans*-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide;
- 2,3-Dihydro-naphthalene-1-carboxylic acid {*trans*-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide;

- 6,7-Dihydro-quinoline-8-carboxylic acid {trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide;
- 9-[2-(trans-4-[[1-(2-Methyl-quinolin-5-yl)-methanoyl]-amino]-cyclohexyl)-ethyl]-1,4-dihydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester;
- 5 9-(2-{trans-4-[3-((S)-1-Naphthalen-1-yl-ethyl)-ureido]-cyclohexyl}-ethyl)-1,4-dihydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester;
- 9-[2-(trans-4-[[1-(2-Methyl-quinolin-5-yl)-methanoyl]-amino]-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester;
- (1S,4R)-9-(2-[4-[(1-Quinolin-5-yl-methanoyl)-amino]-cyclohexyl]-ethyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester;
- 10 9-(2-{trans-4-[3-((S)-1-Naphthalen-1-yl-ethyl)-ureido]-cyclohexyl}-ethyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester;
- 1-(trans-4-{2-[6-(2-Methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-3-((S)-1-naphthalen-1-yl-ethyl)-urea;
- 15 Quinoline-5-carboxylic acid (trans-4-{2-[6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;
- 8-Chloro-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;
- 8-Chloro-2-methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;
- 20 1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;
- 8-Methyl-quinoline-5-carboxylic acid (4-{2-[(1S,4R)-6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;
- 2,8-Dimethyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;
- 1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;
- 25 1-(trans-4-{2-[6-(2-Methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-3-((R)-1-naphthalen-1-yl-ethyl)-urea;
- 1-(trans-4-{2-[6-Butyryl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-3-((S)-1-naphthalen-1-yl-ethyl)-urea;
- Quinoline-5-carboxylic acid (trans-4-{2-[6-butyryl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;
- 30 8-Chloro-2-methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-butyryl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;
- Quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;

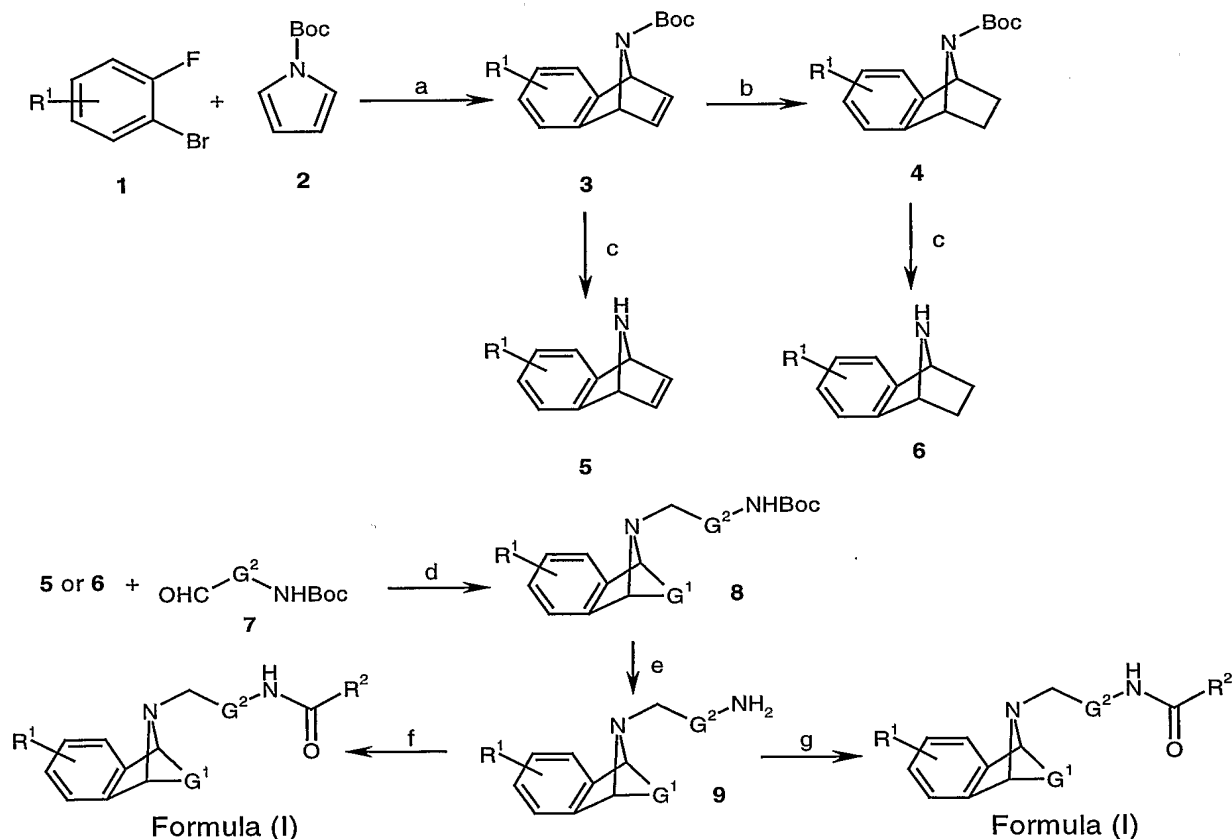
- 1-((S)-1-Naphthalen-1-yl-ethyl)-3-(trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-urea;  
 8-Methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;  
 5 2,8-Dimethyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;  
 8-Methoxy-2-methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide;  
 1-((R)-1-Naphthalen-1-yl-ethyl)-3-(4-{2-[(1S,4R)-6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-urea;  
 10 Quinoline-5-carboxylic acid methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide 8-Methyl-quinoline-5-carboxylic acid methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide;  
 15 2,8-Dimethyl-quinoline-5-carboxylic acid methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide;  
 8-Chloro-quinoline-5-carboxylic acid methyl-{4-[(1S,4S)-1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide;  
 8-Chloro-2-methyl-quinoline-5-carboxylic acid methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide and  
 20 pharmaceutically acceptable salts thereof.

### **METHODS OF PREPARATION**

- The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The synthesis provided for these Schemes is applicable for producing compounds of Formula (I) having a variety of different R<sup>1</sup>, R<sup>2</sup>, G<sup>1</sup> and G<sup>2</sup> which are reacted, employing substituents which are suitable protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. Once the bicyclic amine core has been established, further compounds of these Formulas may be prepared by applying techniques for functional groups interconversion, well known in the art. While the Schemes are shown with compounds only of Formula (I), this is merely for illustration purpose only. **Scheme 1**

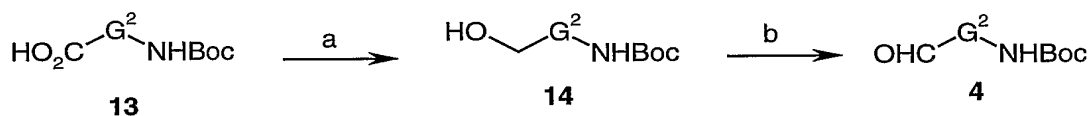
The desired compounds of formula (I) can be prepared as outlined in Scheme 1. Compounds **3** can be obtained via a benzyne reaction from suitable starting materials such as 2-fluorobromobenzenes and suitably N-protected pyrrole using carbamate protecting groups well known in the art such as the Boc group.

- 5 The reaction can be effected using reagents such as magnesium or alkyl lithiums in suitable solvent such as THF or ether. Compounds **5** can be obtained by deprotection of the Boc group using standard methods such as treatment with trifluoroacetic acid (TFA), dry HCl or iodotrimethylsilane (TMSI) in suitable aprotic solvents. The compounds **4** can be prepared by subjecting **3** to standard reductive
- 10 conditions well known to those skilled in the art such as treatment with hydrogen gas in the presence of a catalytic amount of palladium on carbon in a suitable solvent such as ethanol. Deprotection to yield compounds **6** can be effected in a manner similar to that described for compounds **5**. Compounds **8** can be obtained by reacting **5** or **6** with aldehydes **7** under the well known reductive amination
- 15 conditions using suitable reagents such as sodium triacetoxyborohydride. The



Reagents and conditions: a) Mg, THF; b) H<sub>2</sub>, Pd/C, EtOH; c) TFA, CH<sub>2</sub>Cl<sub>2</sub>; d) NaBH(OAc)<sub>3</sub>, (CH<sub>2</sub>Cl)<sub>2</sub>; e) TFA, CH<sub>2</sub>Cl<sub>2</sub>; f) Carboxylic acid **10**, EDC·HCl, HOBT, diisopropylethylamine, CH<sub>2</sub>Cl<sub>2</sub>; g) Amine **11**, triphosgene, CH<sub>2</sub>Cl<sub>2</sub> or Amine **11**, p-NO<sub>2</sub>-PhOCOCl, CH<sub>2</sub>Cl<sub>2</sub> or isocyanate **12**, DMF or **9**, DPPA, DMF.

compounds **9** can then be prepared by deprotection of **8** using the conditions listed for the preparation of the compounds **5**. Compounds of formula (I) which are of the amide type, can be made by treating compounds **9** with carboxylic acids **10** under suitable amide coupling conditions well known to those skilled in the art such as 1-hydroxybenzotriazole hydrate (HOBT), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) and diisopropylethylamine (DIEA) in dichloromethane. . Compounds of formula (I) which are of the urea type, can be made by treating compounds **9** with a suitable coupling reagent such as triphosgene or 4-nitrophenylchloroformate followed by amines **11** or by treating compounds **9** with isocyanates **12**, which may have been formed *in situ* via a Curtius rearrangement effected by exposing carboxylic acids **10** a reagent such as diphenylphosphoryl azide, in a suitable solvent such as DMF.

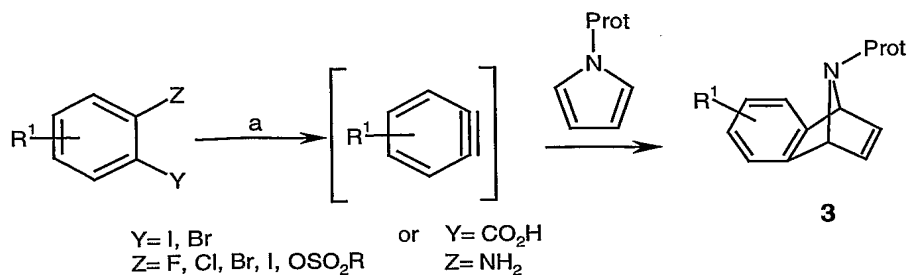


Reagents and conditions: a) BH<sub>3</sub>-THF; b) PCC or TPAP, NMO, 4ÅMs

## Scheme 2

Aldehydes **4** may be prepared from carboxylic acids **13** by reduction to the alcohol **14** using standard conditions such as borane-THF complex (BH<sub>3</sub>-THF) followed by oxidation to the aldehyde using standard conditions well known to those skilled in the art such as pyridinium chlorochromate (PCC), tetrapropylammonium perruthenate (TPAP), Swern oxidation or Dess-Martin periodinane. Alternatively, compounds **4** may be prepared according to Stemp *et al.* (*J. Med. Chem.* **2000**, *43*, 1878-85).

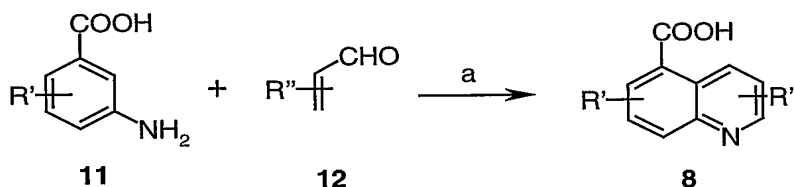




Reagents and conditions: a) Mg or alkyl lithium; b) diazotisation conditions

### Scheme 3

If suitable 2-fluorobromobenzenes are not commercially available, the benzyne reaction to form compounds **3** can be performed with other 1,2-substituted benzenes: 1) For those in which the substituent Y is either iodine or bromine and the substituent Z is any halogen or an aryl sulfonate the benzyne forming reaction may be effected by treatment with either magnesium or an alkyl lithium; 2) For 2-aminobenzoic acids, the benzyne may be formed by subjecting the substrate to diazotisation reagents well known in the art such as isoamyl nitrite or sodium nitrite in acidic media.

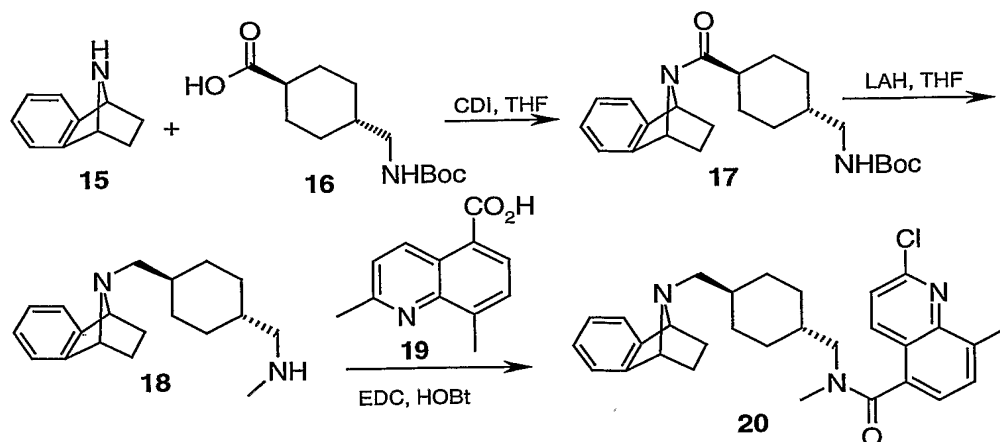


Reagents and conditions: a) 9N HCl, ferrous sulfate, sodium 3-nitrobenzenesulfonate

### Scheme 4

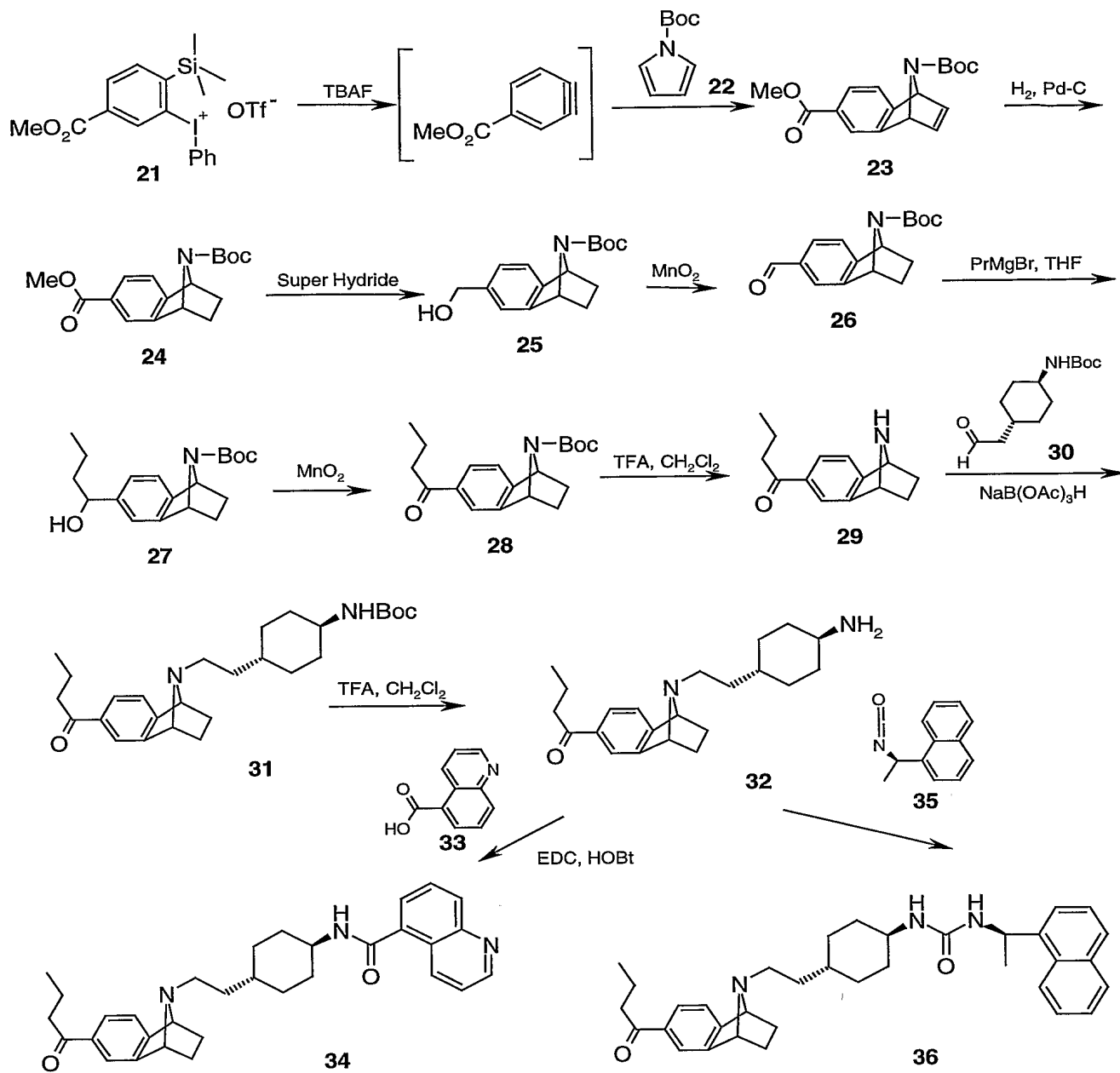
If the required acid **8** is of the quinoline-5-carboxylic acid-type, it can be prepared as outlined in Scheme 3. The 3-amino-benzolic acid **11** can be converted to quinoline-5-carboxylic acid **8** by condensing with a suitable propenal **12**. Otherwise, non-commercially available acids **8** can be prepared as described by Hadley *et al.* (WO 00/21951).

A more specific preparation method leading to compounds with Formula (I) is outlined in **Scheme 5**. 1,1'-Carbonyldiimidazole (CDI) mediated condensation of amine **15** with acid **16** provided amide **17**. Reduction with lithium aluminium hydride (LAH) afforded amine **18** that was coupled with acid **19** under suitable amide formation conditions well known to those skilled in the art such as EDC and HOBt to generate compound **20**.

**Scheme 5**

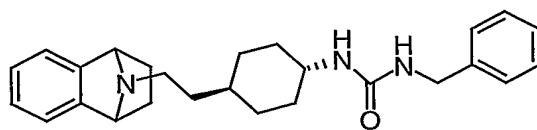
A more specific preparation method leading to compounds with Formula (I) is outlined in **Scheme 6**. Starting with benzyne formation from **21**, coupling with pyrrole **22** provided **23**. Reduction of the olefine with H<sub>2</sub> followed by reduction of the ester with super hydride and oxidation of the resultant alcohol with MnO<sub>2</sub> then afforded aldehyde **26**. Addition of CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>MgBr followed by oxidation with MnO<sub>2</sub> and deprotection with TFA furnished bicyclic amine **29**. Condensation with aldehyde **30**, reduction of the resultant imine with NaBH(OAc)<sub>3</sub> and deprotection with TFA generated primary amine **32**. It was conveniently converted to amide **34** or urea **36**.

**Scheme 6**



### SYNTHETIC EXAMPLES

#### 5 Example 1



1-Benzyl-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea

1a) {4-[2-(1,2,3,4-Tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-carbamic acid *tert*-butyl ester

To a solution of 1,2,3,4-tetrahydro-1,4-epiazano-naphthalene (prepared to *J. of Organic Chemistry*, **1966**, *31*, 764-767) (1.237g, 8.52mmol) in 75mL of 1,2-dichloroethane, [4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (2.056g, 8.52mmol) and sodium triacetoxyborohydride (2.708g, 12.78mmol) were added. The mixture was stirred at RT overnight, diluted with dichloromethane. The resulting mixture was washed with saturated aqueous K<sub>2</sub>CO<sub>3</sub>, extracted with dichloromethane, dried over magnesium sulfate and removed the solvent *in vacuo*. The resulting crude was purified via filtering through a silica pad using ethyl acetate as mobile phase to give 2.681g (85%) of the title compound. LCMS m/z 371.2 (M+H).

1b) 4-[2-(1,2,3,4-Tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine

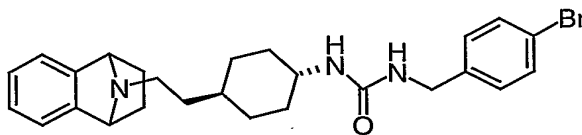
To the solution of the crude {4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-carbamic acid *tert*-butyl ester (2.681g, 7.23mmol) in 60mL of dichloromethane was added 4.5mL of TFA. The mixture was stirred at RT overnight. The solvent was evaporated to give the crude TFA salt. This material was partitioned between saturated aqueous K<sub>2</sub>CO<sub>3</sub> and CH<sub>2</sub>Cl<sub>2</sub>. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2X). The combined organic phase was washed with brine, dried over magnesium sulfate and removed the solvent *in vacuo* to give the title compound 1.759g (90%). LCMS m/z 271.2 (M+H).

1c) 1-Benzyl-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea

The mixture of 4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine (137mg, 0.51mmol) and benzyl isocyanate (63  $\mu$ L, 0.51mmol) in

1.4mL of DMF was stirred at RT overnight. Solid precipitated out of the solution. The mixture was filtered, the solid was washed with ethyl acetate and hexane to yield the title compound 131mg (65%) as a white solid. LCMS m/z 404.2 (M+H).

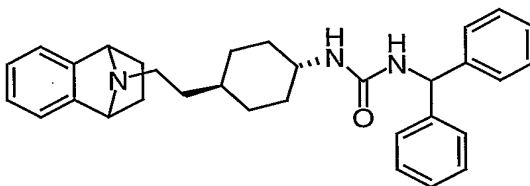
## 5 Example 2



1-(4-Bromo-benzyl)-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea

- 10 Following the general procedure described in Example 1c, 4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine (76mg, 0.28mmol) coupled with 4-bromo-benzyl isocyanate (40μL, 0.28mmol) to give the titled compound 37mg (28%). LCMS m/z 482.0 (M+H).

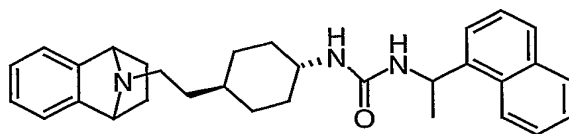
## 15 Example 3



1-(1,1-Diphenyl-methyl)-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea

- 20 The mixture of 4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine (68mg, 0.25mmol) and diphenylmethyl isocyanate (48μL, 0.25mmol) in 1.0mL of DMF was stirred at RT overnight. The mixture was diluted with ethyl acetate, washed with water (2X) and dried over magnesium sulfate. Removal of the solvent *in vacuo* and recrystallization from ethyl acetate/hexane
- 25 gave the titled compound 55mg (46%). LCMS m/z 480.2 (M+H).

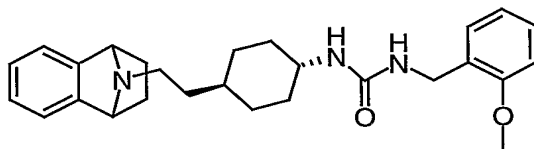
## Example 4



1-(1-Naphthalen-1-yl-ethyl)-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea

- 5 Following the general procedure described in Example 3, 4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine (75mg, 0.28mmol) coupled with 1-(1-naphthyl)ethyl isocyanate (49 $\mu$ L, 0.28mmol) to give the titled compound 62mg (52%). LCMS m/z 468.4 (M+H).

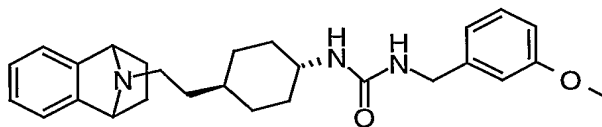
#### 10 Example 5



1-(2-Methoxy-benzyl)-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea

- 15 Following the general procedure described in Example 1c, 4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine (66mg, 0.24mmol) coupled with 2-methoxy-benzyl isocyanate (38 $\mu$ L, 0.24mmol) to give the titled compound 72mg (72%). LCMS m/z 434.4 (M+H).

#### 20 Example 6

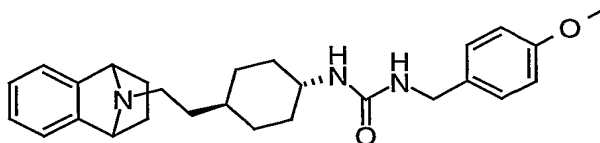


1-(3-Methoxy-benzyl)-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea

- 25 Following the general procedure described in Example 1c, 4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine (67mg, 0.25mmol) coupled

with 3-methoxy-benzyl isocyanate (36 $\mu$ L, 0.25mmol) to give the titled compound 31mg (31%). LCMS m/z 434.4 (M+H).

### Example 7



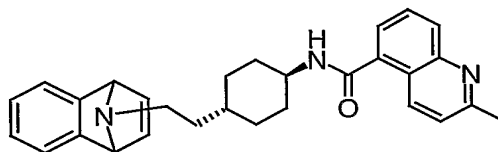
5

1-(4-Methoxy-benzyl)-3-{4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-urea

Following the general procedure described in Example 1c, 4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine (77mg, 0.28mmol) coupled with 4-methoxy-benzyl isocyanate (41 $\mu$ L, 0.28mmol) to give the titled compound 49mg (%). LCMS m/z 434.4 (M+H).

10

### Example 8



15

2-Methyl-quinoline-5-carboxylic acid {4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide

8a) {4-[2-(1,4-Dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-carbamic acid *tert*-butyl ester

20

Following the procedure outlined in Example 1a, 1,4-dihydro-1,4-epiazano-naphthalene, which was made according to *J. of Organic Chemistry*, **1966**, *31*, 764-767, (825mg, 5.73mmol) was treated with [4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (1.38g, 5.73mmol) in the presence of sodium triacetoxyborohydride (1.81g, 8.57mmol) to afford the crude material. Flash chromatography on silica gel eluting with methanol / dichloromethane (5/95, v/v) to give 1.52g (72%) of the title compound. LCMS m/z 369 (M+H).

25

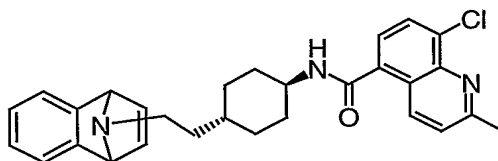
## 8b) 4-[2-(1,4-Dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine

The mixture of {4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-carbamic acid *tert*-butyl ester (760mg, 2.14mmol) and iodotrimethylsilane (455μL, 3.2mmol) in 10mL of chloroform was stirred at RT for 2h. Removal the solvent *in vacuo* yielded the crude material 0.89g, which was used in the next step without further purification.

## 8c) 2-Methyl-quinoline-5-carboxylic acid {4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide

To a mixture of 4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine (150mg, 0.59mmol), DIEA (514 μL, 2.95mmol) and 2-methyl-quinoline-5-carboxylic acid (145mg, 0.65mmol) in 15mL of chloroform were added EDC (113mg, 0.55mmol) and HOBt (8mg, 0.059mmol). The mixture was stirred at RT overnight. The solvent was removed *in vacuo* to yield the crude product. Purification upon Gilson HPLC, eluting with acetonitrile/water/0.1% TFA (10/90, v/v to 70/30, v/v, over 10min), gave the desired product 232mg (90%). LCMS: m/z 438 (M+H).

20

**Example 9**8-Chloro-2-methyl-quinoline-5-carboxylic acid {4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide

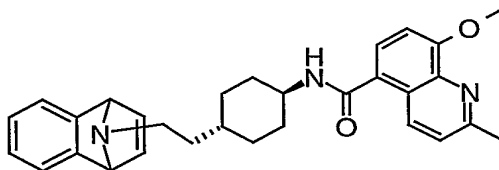
25

Following the general procedure outlined in Example 8c, 4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine (150mg, 0.59mmol) coupled with 8-chloro-2-methyl-quinoline-5-carboxylic acid (167mg, 0.65mmol) to afford the title compound 18mg. LCMS 472 (M+H).

30

**Example 10**

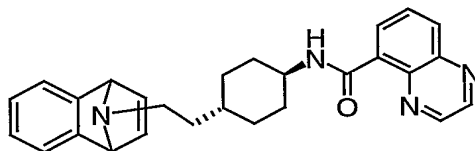




8-Methoxy-2-methyl-quinoline-5-carboxylic acid {4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide

- 5 Following the general procedure outlined in Example 8c, 4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine (150mg, 0.59mmol) coupled with 8-methoxy-2-methyl-quinoline-5-carboxylic acid (165mg, 0.64mmol) to afford the title compound 266mg (96%). LCMS 468 (M+H).

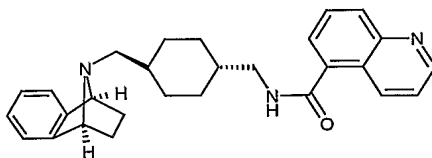
#### 10 Example 11



Quinoxaline-5-carboxylic acid {4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide

- 15 Following the general procedure outlined in Example 8c, 4-[2-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine (100mg, 0.37mmol) coupled with quinoxaline-5-carboxylic acid (71mg, 0.41mmol) to afford the title compound 117mg (74%). LCMS 425 (M+H).

#### 20 Example 12



Quinoline-5-carboxylic acid {trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide

- 12a) Preparation of [trans-4-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl-methanoyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester
- 25

To a solution of *trans*-4-[[[(1,1-dimethylethyl)oxy]carbonyl]amino)methyl]cyclohexanecarboxylic acid (1.9 g, 7.6 mmol) in THF (10 mL), 1,1'-carbonyldiimidazole (1.2 mL, 7.6 mmol) was added. The mixture was stirred at room temperature for 30 minutes before 1,2,3,4-tetrahydro-1,4-epiazano-naphthalene (1.0 g, 6.9 mmol) was added. The resultant solution was stirred at room temperature for 3 hours, diluted with EtOAc (50 mL), and washed with H<sub>2</sub>O (30 mL) and brine (30 mL). The organic phases were collected, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Flash chromatography (hexane / ethyl acetate, 1:1) then afforded the title compound (1.8 g, 67%): LCMS (ES) *m/z* 385 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.01 (m, 2H), 1.42 (m, 4H), 1.46 (s, 9H), 1.63 (m, 2H), 1.85 (m, 3H), 2.12 (m, 2H), 2.42 (m, 1H), 3.00 (m, 2H), 4.58 (s, br, 1H), 5.19 (s, br, 1H), 5.60 (s, br, 2H), 7.17 (m, 2H), 7.27 (m, 2H).

12b) Preparation of 1-(*trans*-4-aminomethyl-cyclohexyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl-methanone

To a solution of [trans-4-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl-methanoyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester (0.95 g, 2.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), trifluoroacetic acid (1.9 mL, 25 mmol) was added. The solution was stirred at room temperature for 4 hours before CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added followed by Et<sub>3</sub>N (5 mL). The resultant mixture was then washed with H<sub>2</sub>O (30 mL), NaOH (1N, 30 mL) and brine (30 mL). The organic phases were collected, dried over K<sub>2</sub>CO<sub>3</sub>, filtered and concentrated to afford the title compound (0.57 g, 82%); LCMS (ES) *m/z* 285 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.95 (m, 2H), 1.42 (m, 4H), 1.58 (m, 2H), 1.83 (m, 3H), 2.13 (m, 2H), 2.32 (m, 1H), 2.56 (m, 2H), 5.19 (s, 1H), 5.58 (s, 2H), 7.17 (m, 2H), 7.27 (m, 2H).

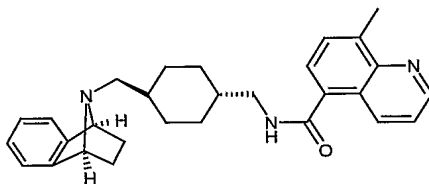
12c) Preparation of *C*-{trans-4-[1-(1,2,3,4-Tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexyl}-methylamine

To a solution of 1-(*trans*-4-aminomethyl-cyclohexyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl-methanone (0.25 g, 0.88 mmol) in THF (2.0 mL), lithium aluminumhydride (1.0 N in THF, 2.6 mL, 2.6 mmol) was added. The solution was heated with a microwave reactor at 80°C for 60 minutes before it was mixed with saturated aqueous Na<sub>2</sub>SO<sub>4</sub> solution. The resultant mixture was filtered through celite. The organic phases were collected, dried over K<sub>2</sub>CO<sub>3</sub>, filtered and concentrated to afford the title compound (0.21 g, 88%): LCMS (ES) *m/z* 271 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.88 (m, 4H), 1.30 (m, 6H), 1.82 (m, 4H), 1.97 (m, 2H), 2.12 (m, 2H), 2.52 (m, 2H), 4.15 (s, 2H), 7.13 (m, 2H), 7.22 (m, 2H).

12d) Preparation of quinoline-5-carboxylic acid {*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide

A solution of *C*-{*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexyl}-methylamine (30 mg, 0.111 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was mixed with 5-quinolinecarboxylic acid (21.1 mg, 0.122 mmol), EDC (23.4 mg, 0.122 mmol), HOBt (1.5 mg, 0.011 mmol) and Et<sub>3</sub>N (0.109 mL, 0.777 mmol). The solution was stirred for 20 hours and concentrated. The resultant residue was dissolved in DMSO and purification via a reverse phase HPLC then afforded the title compound (67.5 mg, 93%): LCMS (ES) *m/z* 426 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.05 (m, 4H), 1.61 (m, 4H), 1.84 (m, 4H), 2.63 (m, 4H), 3.40 (m, 2H), 5.07 (s, 2H), 7.44 (s, 4H), 8.01 (m, 3H), 8.54 (m, 1H), 9.17 (m, 1H), 9.52 (d, 1H).

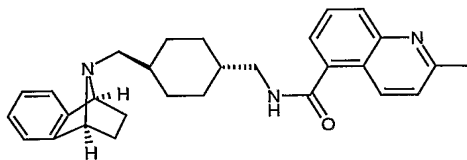
### Example 13



15 8-Methyl-quinoline-5-carboxylic acid {*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide

The title compound was prepared from *C*-{*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexyl}-methylamine and 8-methyl-quinoline-5-carboxylic acid by following the experimental procedure in Example 12d (97% yield): LCMS (ES) *m/z* 440 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.04 (m, 4H), 1.61 (m, 4H), 1.85 (m, 4H), 2.63 (m, 2H), 2.72 (m, 2H), 2.95 (s, 3H), 3.40 (m, 2H), 5.05 (s, 2H), 7.44 (s, 4H), 7.87 (d, 1H), 7.99 (m, 2H), 9.33 (m, 1H), 9.60 (d, 1H).

### Example 14



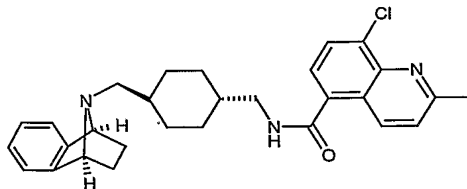
25

2-Methyl-quinoline-5-carboxylic acid {*trans*-4-[(1*S*,4*S*)-1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide

The title compound was prepared from *C*-{*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexyl}-methylamine and 2-methyl-quinoline-

5-carboxylic acid by following the experimental procedure in Example 12d (77% yield): LCMS (ES)  $m/z$  440 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.01 (m, 4H), 1.61 (m, 4H), 1.83 (m, 4H), 2.65 (m, 4H), 3.07 (s, 3H), 3.38 (m, 2H), 5.07 (s, 2H), 7.45 (s, 4H), 7.73 (d, 1H), 7.96 (m, 2H), 8.45 (m, 1H), 9.35 (d, 1H).

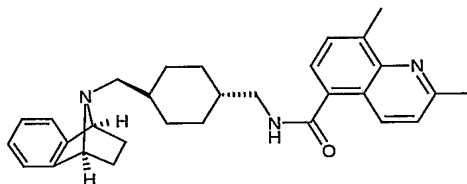
5

**Example 15**

10 8-Chloro-2-methyl-quinoline-5-carboxylic acid {*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide

The title compound was prepared from *C*-{*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexyl}-methylamine and 8-chloro-2-methyl-quinoline-5-carboxylic acid by following the experimental procedure in Example 12d (79% yield): LCMS (ES)  $m/z$  474 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.00 (m, 4H), 1.59 (m, 4H), 1.82 (m, 4H), 2.60 (m, 2H), 2.68 (m, 2H), 3.02 (s, 3H), 3.35 (m, 2H), 5.05 (s, 2H), 7.43 (s, 4H), 7.66 (d, 1H), 7.76 (d, 1H), 7.88 (d, 1H), 9.07 (d, 1H).

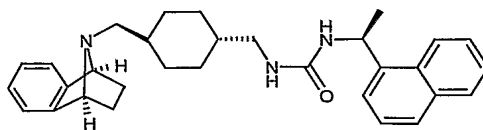
15

**Example 16**

20 2,8-Dimethyl-quinoline-5-carboxylic acid {*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide

The title compound was prepared from *C*-{*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexyl}-methylamine and 2,8-dimethyl-quinoline-5-carboxylic acid by following the experimental procedure in Example 12d (83% yield): LCMS (ES)  $m/z$  454 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.05 (m, 4H), 1.62 (m, 4H), 1.84 (m, 4H), 2.76 (m, 4H), 2.91 (s, 3H), 3.13 (s, 3H), 3.38 (m, 2H), 5.06 (s, 2H), 7.43 (s, 4H), 7.81 (m, 2H), 9.43 (m, 1H), 10.44 (m, 1H).

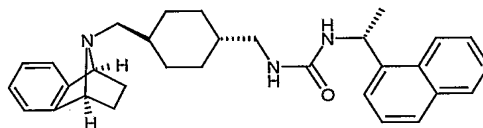
25

**Example 17**

1-((S)-1-Naphthalen-1-yl-ethyl)-3-{*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-urea

- 5           A solution of *C*-{*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexyl}-methylamine (30 mg, 0.111 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was mixed with 1-[(1*S*)-1-isocyanatoethyl]naphthalene (24 mg, 0.122mmol) and stirred at room temperature for 3 hours. The solution was concentrated, redissolved in DMSO and filtered. Purification via a reverse phase HPLC then afforded the title
- 10 compound (39.2 mg, 76%): LCMS (ES) *m/z* 468 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.72 (m, 4H), 1.02 (m, 2H), 1.51 (m, 8H), 1.66 (d, 3H), 2.45 (m, 2H), 2.64 (m, 3H), 2.81 (m, 1H), 2.92 (m, 1H), 4.84 (s, 1H), 4.90 (s, 1H), 5.45 (s, br, 1H), 7.40 (s, 4H), 7.52 (m, 4H), 7.82 (d, 1H), 7.91 (d, 1H), 8.10 (d, 1H).

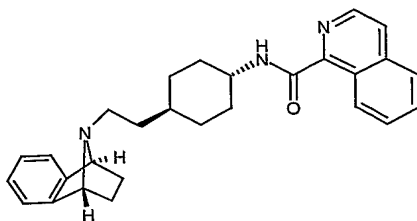
15   **Example 18**



1-((R)-1-Naphthalen-1-yl-ethyl)-3-{*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-urea

- 20           The title compound was prepared from *C*-{*trans*-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexyl}-methylamine and 1-[(1*S*)-1-isocyanatoethyl]naphthalene by following the experimental procedure in Example 17 (80% yield): LCMS (ES) *m/z* 468 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.71 (m, 4H), 1.00 (m, 2H), 1.55 (m, 8H), 1.68 (d, 3H), 2.49 (m, 2H), 2.67 (m, 3H), 2.81 (m, 1H), 2.93 (m, 1H), 4.92 (s, 1H), 4.94 (s, 1H), 5.41 (s, br, 1H), 7.41 (s, 4H), 7.53 (m, 4H), 7.83
- 25 (d, 1H), 7.92 (d, 1H), 8.08 (d, 1H).

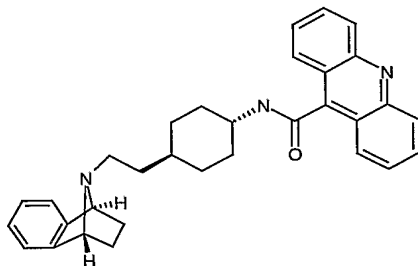
**Example 19**



Isoquinoline-1-carboxylic acid {*trans*-4-[(1*S*,4*R*)-2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide

A solution of *trans*-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine (40 mg, 0.15 mmol) in CHCl<sub>3</sub> (5 mL) was mixed with isoquinoline-1-carboxylic acid (28 mg, 0.16 mmol), EDC (28 mg, 0.15 mmol), HOBT (2 mg, 0.015 mmol) and DIEA (0.129 mL, 0.742 mmol). The resultant mixture was stirred at room temperature overnight, filtered and concentrated. Purification via a reverse phase HPLC then afforded the title compound (6 mg, 10%): LCMS (ES) *m/z* 426 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.1 (m, 2H), 1.3 (m, 4H), 1.4 (m, 2H), 1.8 (m, 2H), 2.12 (m, 2H), 2.28 (m, 4H), 2.42 (m, 1H), 3.94 (m, 1H), 4.30 (s, 2H), 7.19 (m, 2H), 7.25 (m, 1H), 7.70 (m, 2H), 7.78 (d, 1H), 7.86 (d, 1H), 7.99 (d, 1H), 8.4(d, 1H), 9.6 (d, 1H).

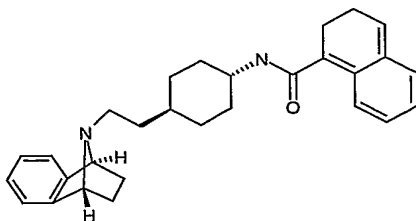
**Example 20**



Acridine-9-carboxylic acid {*trans*-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide

The title compound was prepared from *trans*-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine and acridine-9-carboxylic acid by following the procedures in Example 19 (7% yield): LCMS (ES) *m/z* 476 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.9 (m, 2H), 1.31 (m, 7H), 1.47 (m, 2H), 1.81 (d, 2H), 2.20 (m, 2H), 2.28 (m, 2H), 4.26 (m, 3H), 6.10 (d, 1H), 7.22 (m, 2H), 7.31 (m, 2H), 7.55 (m, 2H), 7.77 (m, 2H), 8.02(d, 2H), 8.18 (d, 2H).

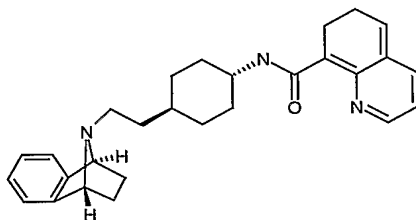
**Example 21**



2,3-Dihydro-naphthalene-1-carboxylic acid {trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide

A solution of trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine (60 mg, 0.22 mmol) in  $\text{CHCl}_3$  (3 mL) was mixed with naphthalene-1-carbonyl chloride (0.037 mL, 0.24 mmol) and  $\text{Et}_3\text{N}$  (0.1 mL, 0.72 mmol). The resultant mixture was stirred at room temperature overnight and concentrated. Purification via a reverse phase HPLC then afforded the title compound (34 mg, 36%): LCMS (ES)  $m/z$  425 ( $\text{M}+\text{H}^+$ );  $^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  1.22 (m, 6H), 1.57 (m, 3H), 1.69 (m, 2H), 2.10 (d, 2H), 2.62 (m, 2H), 2.77 (m, 2H), 3.96 (m, 1H), 5.03 (s, 2H), 6.01 (d, 1H), 7.43 (m, 5H), 7.53 (m, 3H), 7.88 (m, 2H), 8.21 (d, 1H).

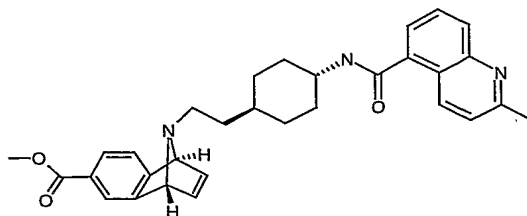
**Example 22**



6,7-Dihydro-quinoline-8-carboxylic acid {trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-amide

The title compound was prepared from trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexylamine and quinoline-8-carboxylic acid by following the procedures in Example 19 (44%): LCMS (ES)  $m/z$  426 ( $\text{M}+\text{H}^+$ );  $^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$  1.33 (m, 9H), 1.77 (d, 2H), 2.18 (m, 6H), 4.04 (m, 1H), 4.21 (s, 2H), 7.18 (m, 2H), 7.25 (m, 2H), 7.48 (t, 1H), 7.67 (t, 1H), 7.95 (d, 1H), 8.28 (d, 1H), 8.90 (m, 2H).

**Example 23**



9-[2-(trans-4-{[1-(2-Methyl-quinolin-5-yl)-methanoyl]-amino}-cyclohexyl)-ethyl]-1,4-dihydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester

23a) Preparation of 1,4-dihydro-1,4-epiazano-naphthalene-6,9-dicarboxylic acid 9-*tert*-butyl ester 6-methyl ester

A solution of [5-(methoxycarbonyl)-2-(trimethylsilyl)phenyl]-(phenyl)iodonium triflate (7.1 g, 12.7 mmol) and pyrrole-1-carboxylic acid *tert*-butyl ester (10.6 mL, 63.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was cooled to 0°C and added by a THF solution of Bu<sub>4</sub>NF (16.5 mL, 1 M in THF, 16.5 mmol). The mixture was stirred for 30 min. Water was added to the mixture, and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were collected, dried over MgSO<sub>4</sub> and concentrated. Flash chromatography then afforded the title compound (3.0 g, 78.7%): LCMS (ES) *m/z* 302 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.37 (s, 9H), 3.89 (s, 3H), 5.52 (s, br, 2H), 6.89 (s, br, 2H), 7.34 (m, 1H), 7.71 (m, 1H), 7.89 (s, 1H).

23b) Preparation of 1,4-dihydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester

A solution of 1,4-dihydro-1,4-epiazano-naphthalene-6,9-dicarboxylic acid 9-*tert*-butyl ester 6-methyl ester (1 g, 3.31 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was mixed with TFA (2.25 mL, 29.2 mmol) at 0°C. The mixture was stirred at room temperature overnight, diluted with EtOAc (15 mL) and concentrated. The resultant residue was extracted with aqueous NaOH solution (2N, 20 mL), H<sub>2</sub>O (50 mL) and brine (50 mL). The organic phases were collected, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford the title compound (0.5 g, 75%): LCMS (ES) *m/z* 202 (M+H)<sup>+</sup>.

23c) Preparation of 9-[2-(trans-4-*tert*-Butoxycarbonylamino-cyclohexyl)-ethyl]-1,4-dihydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester

A solution of 1,4-dihydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester (0.5 g, 2.48 mmol) in 1,2-dichloroethane (25 mL) was mixed with 3,3-dimethyl-*N*-[4-(2-oxo-ethyl)-cyclohexyl]-butyramide (0.6 g, 2.49 mmol) and NaB(OAc)<sub>3</sub>H (0.84 g, 3.96 mmol). The mixture was stirred at room temperature overnight and diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The solution was extracted with saturated aqueous NaHCO<sub>3</sub> solution (50 mL) and brine (50 mL). The organic phases were collected,



dried over  $\text{MgSO}_4$ , and concentrated to afford the title compound (0.9 g, 85%); MS (ES)  $m/z$  427 ( $\text{M}+\text{H}$ )<sup>+</sup>.

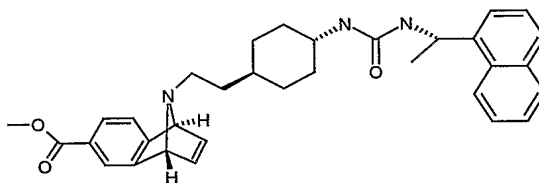
23d) Preparation of 9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,4-dihydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester

5 The title compound was prepared from 9-[2-(trans-4-tert-butoxycarbonylamino-cyclohexyl)-ethyl]-1,4-dihydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester by following the procedure in Example 23b (36%): LCMS (ES)  $m/z$  327 ( $\text{M}+\text{H}$ )<sup>+</sup>.

23e) Preparation of 9-[2-(trans-4-[[1-(2-methyl-quinolin-5-yl)-methanoyl]-amino]-cyclohexyl)-ethyl]-1,4-dihydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester

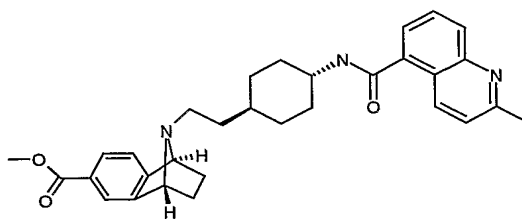
The title compound was prepared from 9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,4-dihydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester and quinoline-5-carboxylic acid by following the procedures in Example 19 (73% yield):  
 15 LCMS (ES)  $m/z$  496 ( $\text{M}+\text{H}$ )<sup>+</sup>; <sup>1</sup>H-NMR( $\text{CDCl}_3$ )  $\delta$  1.19 (m, 5H), 1.58 (m, 2H), 1.71 (m, 2H), 2.14 (m, 2H), 2.87 (m, 2H), 3.07 (s, 3H), 3.97 (m, 4H), 5.52 (m, 2H), 6.35 (d, 1H), 7.15 (m, 2H), 7.61 (d, 1H), 7.69 (d, 1H), 7.95 (m, 2H), 8.06 (d, 2H), 8.15 (s, 1H), 8.59 (d, 1H), 9.35 (d, 1H).

## 20 Example 24



9-(2-{trans-4-[3-((S)-1-Naphthalen-1-yl-ethyl)-ureido]-cyclohexyl}-ethyl)-1,4-dihydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester

The title compound was prepared from 9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,4-dihydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester and 1-((S)-1-isocyanato-ethyl)-naphthalene by following the procedure in Example 17 (50%): LCMS (ES)  $m/z$  524 ( $\text{M}+\text{H}$ )<sup>+</sup>; <sup>1</sup>H-NMR( $\text{CDCl}_3$ )  $\delta$  0.90 (m, 3H), 1.27 (m, 2H), 1.50 (m, 4H), 1.65 (d, 3H), 1.75 (m, 1H), 1.88 (m, 1H), 2.71 (m, 2H), 3.35 (m, 1H), 3.91 (m, 1H), 3.96 (s, 3H), 4.40 (s, br, 1H), 5.35 (m, 2H), 5.55 (m, 1H), 7.03 (m, 2H), 7.55 (m, 5H), 7.78 (m, 1H), 7.88 (m, 1H), 8.00 (m, 1H), 8.07 (d, 1H), 8.13 (d, 1H).

**Example 25**

9-[2-(trans-4-{[1-(2-Methyl-quinolin-5-yl)-methanoyl]-amino}-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester

- 5 25a) Preparation of 9-[2-(trans-4-*tert*-butoxycarbonylamino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester

A solution of 9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,4-dihydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester (0.4 g, 0.94 mmol) in ethanol (5 mL) was mixed with 10% Pd/C (45 mg). The mixture was stirred in the presence  
 10 of H<sub>2</sub> (55 psi) at room temperature for 3 hours, filtered through celite and concentrated to afford the title compound (0.24 g, 60%): LCMS (ES) *m/z* 429 (M+H)<sup>+</sup>.

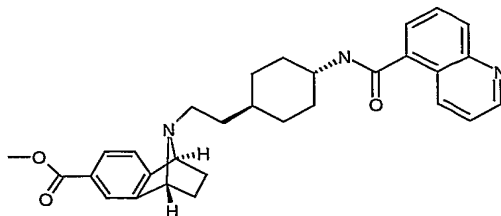
25b) Preparation of 9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester

- 15 The title compound was prepared from 9-[2-(trans-4-*tert*-butoxycarbonylamino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester by following the procedures in Example 23b (60%): LCMS (ES) *m/z* 329 (M+H)<sup>+</sup>.

- 20 25c) Preparation of 9-[2-(trans-4-{[1-(2-methyl-quinolin-5-yl)-methanoyl]-amino}-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester

The title compound was prepared from 9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester and 2-methyl-quinoline-5-carboxylic acid by following the procedures in Example 19  
 25 (26% yield): LCMS (ES) *m/z* 498 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 1.08 (m, 2H), 1.27 (m, 3H), 1.60 (m, 4H), 1.73 (m, 2H), 2.11 (m, 2H), 2.71 (m, 2H), 2.79 (m, 2H), 3.05 (s, 3H), 3.94 (m, 1H), 3.98 (s, 3H), 5.12 (s, 2H), 6.6 (m, 1H), 7.56 (d, 1H), 7.69 (d, 1H), 7.93 (m, 2H), 8.12 (s, 1H), 8.18 (d, 1H), 8.50 (s, 1H), 9.35 (d, 1H).

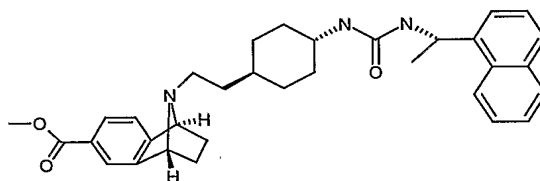
30 **Example 26**



(1S,4R)-9-(2-{4-[(1-Quinolin-5-yl-methanoyl)-amino]-cyclohexyl}-ethyl)-1,2,3,4-tetrahydro-1,4-epiaza no-naphthalene-6-carboxylic acid methyl ester

The title compound was prepared from 9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester and quinoline-5-carboxylic acid by following the procedures in Example 19 (92% yield): LCMS (ES)  $m/z$  484 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.09 (m, 2H), 1.27 (m, 3H), 1.58 (m, 4H), 1.72 (m, 2H), 2.14 (m, 2H), 2.72 (m, 2H), 2.78 (m, 2H), 3.94 (m, 1H), 3.97 (s, 3H), 5.12 (s, 2H), 6.37 (d, 1H), 7.56 (d, 1H), 7.95 (m, 3H), 8.12 (m, 1H), 8.18 (d, 1H), 8.56 (d, 1H), 9.23 (d, 1H), 9.43 (d, 1H).

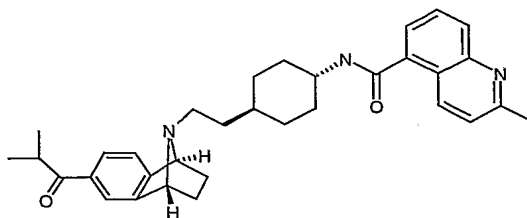
**Example 27**



9-(2-{trans-4-[3-((S)-1-Naphthalen-1-yl-ethyl)-ureido]-cyclohexyl}-ethyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester

The title compound was prepared from 9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6-carboxylic acid methyl ester and 1-((S)-1-isocyanato-ethyl)-naphthalene by following the procedure in Example 17 (41% yield): LCMS (ES)  $m/z$  526 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  0.89 (m, 5H), 1.07 (m, 1H), 1.27 (m, 2H), 1.49 (m, 5H), 1.64 (m, 3H), 1.79 (m, 1H), 1.88 (m, 1H), 2.66 (m, 4H), 3.37 (m, 1H), 3.97 (s, 3H), 4.92 (m, 2H), 5.59 (m, 1H), 7.55 (m, 4H), 7.77 (d, 1H), 7.89 (d, 1H), 8.06 (d, 1H), 8.15 (m, 2H).

**Example 28**



2-Methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

28a) Preparation of 2-ethyl-1-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl-propan-1-one

The title compound was prepared from 6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-9-carboxylic acid *tert*-butyl ester by following the procedure in Example 23b (77% yield): LCMS (ES)  $m/z$  431 (2M+H)<sup>+</sup>.

28b) Preparation of (trans-4-{2-[6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-carbamic acid *tert*-butyl ester

The title compound was prepared from 2-ethyl-1-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl-propan-1-one by following the procedures in Example 23c (39% yield): LCMS (ES)  $m/z$  441 (M+H)<sup>+</sup>.

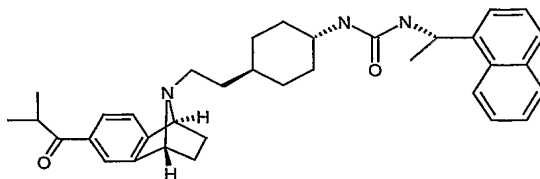
28c) Preparation of 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-methyl-propan-1-one

The title compound was prepared from (trans-4-{2-[6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-carbamic acid *tert*-butyl ester by following the procedure in Example 23b (97% yield): LCMS (ES)  $m/z$  341 (M+H)<sup>+</sup>.

28d) Preparation of 2-methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-methyl-propan-1-one and 2-methyl-quinoline-5-carboxylic acid by following the procedures in Example 19 (69% yield): LCMS (ES)  $m/z$  510 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.09 (m, 2H), 1.27 (m, 8H), 1.61 (m, 4H), 1.74 (m, 2H), 2.13 (m, 2H), 2.38 (m, 1H), 2.71 (m, 2H), 2.81 (m, 2H), 3.06 (s, 3H), 3.56 (m, 1H), 4.0 (m, 1H), 5.14 (s, 2H), 6.48 (d, 1H), 7.20 (m, 1H), 7.58 (d, 1H), 7.70 (d, 1H), 7.95 (m, 2H), 8.06 (d, 1H), 8.53 (d, 1H), 9.37 (d, 1H).

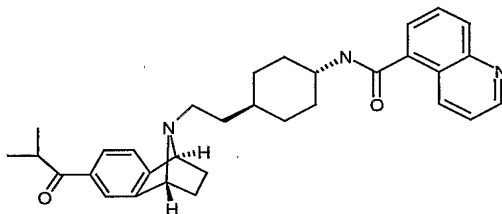
### Example 29



1-(trans-4-{2-[6-(2-Methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-3-((S)-1-naphthalen-1-yl-ethyl)-urea

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-methyl-propan-1-one and 1-((S)-1-isocyanato-ethyl)-naphthalene by following the procedure in Example 17 (51% yield): LCMS (ES)  $m/z$  538 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  0.7 (m, 1H), 0.9 (m, 3H), 1.0 (m, 1H), 1.20 (m, 1H), 1.30 (m, 6H), 1.47 (m, 3H), 1.57 (m, 2H), 1.75 (d, 4H), 1.86 (m, 1H), 2.06 (m, 1H), 2.66 (d, 3H), 3.29 (m, 1H), 3.54 (m, 2H), 4.96 (s, 2H), 5.47 (d, 1H), 7.57 (m, 5H), 7.81 (m, 1H), 7.89 (d, 1H), 8.00 (m, 2H), 8.10 (d, 1H).

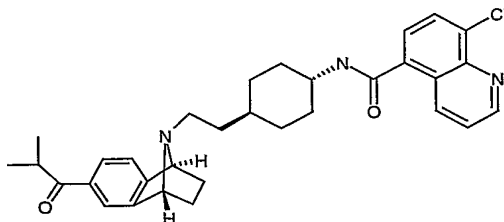
**Example 30**



Quinoline-5-carboxylic acid (trans-4-{2-[6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-methyl-propan-1-one and quinoline-5-carboxylic acid by following the procedures in Example 19 (60% yield): LCMS (ES)  $m/z$  496 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.10 (m, 2H), 1.20 (m, 1H), 1.31 (m, 8H), 1.61 (m, 4H), 1.73 (m, 2H), 2.12 (m, 2H), 2.72 (m, 2H), 2.80 (m, 2H), 3.56 (m, 1H), 3.97 (m, 1H), 5.13 (s, 2H), 6.43 (d, 1H), 7.58 (d, 1H), 7.95 (m, 3H), 8.07 (m, 2H), 8.56 (d, 1H), 9.23 (m, 1H), 9.46 (d, 1H).

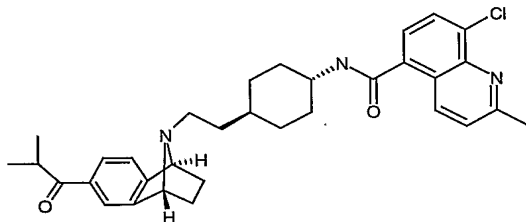
**Example 31**



8-Chloro-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-methyl-propan-1-one and 8-chloro-quinoline-5-carboxylic acid by following the procedures in Example 19 (79% yield): LCMS (ES)  $m/z$  530 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.10 (m, 2H), 1.20 (m, 3H), 1.28 (d, 6H), 1.58 (m, 2H), 1.65 (m, 2H), 1.70 (d, 2H), 2.12 (m, 2H), 2.68 (m, 2H), 2.81 (d, 2H), 3.56 (m, 1H), 3.9 (m, 1H), 5.17 (s, 2H), 6.30 (d, 1H), 7.56 (m, 1H), 7.66 (m, 1H), 7.78 (m, 1H), 7.87 (m, 1H), 7.97 (m, 1H), 8.07 (m, 1H), 9.00 (m, 1H), 9.22 (m, 1H).

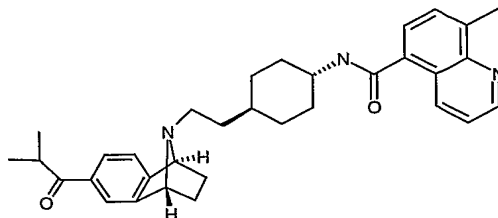
**Example 32**



8-Chloro-2-methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-methyl-propan-1-one and 8-chloro-2-methyl-quinoline-5-carboxylic acid by following the procedures in Example 19 (63% yield): LCMS (ES)  $m/z$  544 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.10 (m, 2H), 1.21 (m, 3H), 1.28 (d, 6H), 1.61 (m, 4H), 1.70 (m, 2H), 2.10 (m, 2H), 2.70 (m, 2H), 2.77 (m, 2H), 2.93 (s, 3H), 3.58 (m, 1H), 3.95 (m, 1H), 5.15 (s, 2H), 6.34 (d, 1H), 7.58 (m, 3H), 7.80 (d, 1H), 8.05 (m, 2H), 8.85 (d, 1H).

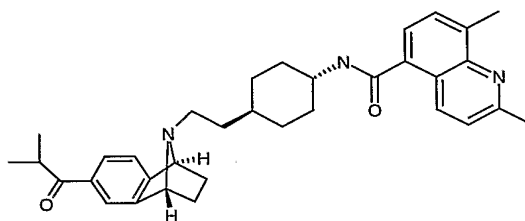
**Example 33**



**8-Methyl-quinoline-5-carboxylic acid (4-{2-[(1S,4R)-6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide**

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-methyl-propan-1-one and 8-methyl-quinoline-5-carboxylic acid by following the procedures in Example 19 (74% yield): LCMS (ES)  $m/z$  510 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.10 (m, 2H), 1.21 (m, 3H), 1.27 (d, 6H), 1.58 (m, 4H), 1.71 (m, 2H), 2.10 (m, 2H), 2.71 (m, 2H), 2.79 (m, 2H), 2.92 (s, 3H), 3.58 (m, 1H), 3.95 (m, 1H), 5.13 (s, 2H), 6.47 (d, 1H), 7.57 (d, 1H), 7.80 (m, 2H), 7.88 (m, 1H), 8.05 (d, 2H), 9.33 (d, 1H), 9.44 (d, 1H).

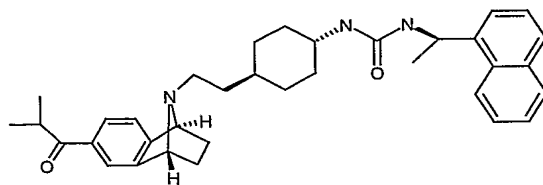
**Example 34**



**2,8-Dimethyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide**

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-methyl-propan-1-one and 2,8-dimethyl-quinoline-5-carboxylic acid by following the procedures in Example 19 (91% yield): LCMS (ES)  $m/z$  524 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.10 (m, 2H), 1.22 (m, 3H), 1.27 (d, 6H), 1.60 (m, 4H), 1.73 (m, 2H), 2.10 (m, 2H), 2.71 (m, 2H), 2.79 (m, 2H), 2.90 (s, 3H), 3.08 (s, 3H), 3.57 (m, 1H), 3.92 (m, 1H), 5.12 (s, 2H), 6.51 (d, 1H), 7.57 (d, 1H), 7.69 (m, 1H), 7.77 (m, 2H), 8.05 (d, 2H), 9.37 (d, 1H).

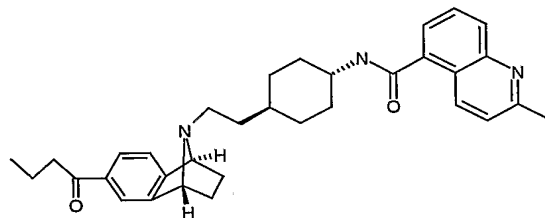
**Example 35**



1-(trans-4-{2-[6-(2-Methyl-propanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-3-((R)-1-naphthalen-1-yl-ethyl)-urea

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-methyl-propan-1-one and 1-((R)-1-isocyanato-ethyl)-naphthalene by following the procedure in Example 17 (48% yield): LCMS (ES)  $m/z$  538 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  0.80 (m, 5H), 1.10 (m, 2H), 1.22 (m, 1H), 1.27 (d, 6H), 1.50 (m, 6H), 1.64 (m, 2H), 1.76 (m, 1H), 1.88 (m, 1H), 2.66 (s, 3H), 3.36 (m, 1H), 3.55 (m, 1H), 4.97 (m, 2H), 5.56 (d, 1H), 7.55 (m, 5H), 7.78 (m, 1H), 7.88 (d, 1H), 8.00 (m, 2H), 8.14 (d, 1H).

### Example 36



2-Methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-butyryl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

36a) Preparation of 1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6,9-dicarboxylic acid 9-*tert*-butyl ester 6-methyl ester

A solution of 1,4-dihydro-1,4-epiazano-naphthalene-6,9-dicarboxylic acid *tert*-butyl ester 6-methyl ester (0.47 g, 1.56 mmol) in ethanol (8 mL) was mixed with Pd/C (10%, 74 mg). The mixture was stirred in the presence of H<sub>2</sub> (55 psi) at room temperature overnight, filtered through celite and concentrated to afford the title compound (0.46 g, 98%): LCMS (ES)  $m/z$  607 ( $2M+H$ )<sup>+</sup>.

36b) Preparation of 6-hydroxymethyl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-9-carboxylic acid 9-*tert*-butyl ester

A solution of 1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-6,9-dicarboxylic acid 9-*tert*-butyl ester 6-methyl ester (0.52 g, 1.71 mmol) in THF (20 mL) was mixed with super hydride (6.8 mL, 1.0M solution in THF, 6.8 mmol) at 0°C. The mixture was stirred at ambient temperature for 2 hours, mixed with HCl (10 mL, 1N), diluted



with brine (50 mL) and extracted with EtOAc (50 mL). The organic phases were collected, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford the title compound (0.47 g, 100%): LCMS (ES) *m/z* 276 (M+H)<sup>+</sup>.

5 36c) Preparation of 6-formyl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-9-carboxylic acid *tert*-butyl ester

A solution of 6-hydroxymethyl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-9-carboxylic acid 9-*tert*-butyl ester (0.47 g, 1.70 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was mixed with Dess-Martin periodinane (0.75 g, 1.77 mmol). The mixture was stirred at r.t. for 2 hours and concentrated. Flash chromatography (Hexane : EtOAc, 4 : 1) then  
10 afforded the title compound (0.40 g, 85%): MS (ES) *m/z* 274 (M+H)<sup>+</sup>.

36d) Preparation of 6-(1-hydroxy-butyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-9-carboxylic acid *tert*-butyl ester

A solution of 6-formyl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-9-carboxylic acid 9-*tert*-butyl ester (0.40 g, 1.46 mmol) in THF (20 mL) was mixed  
15 with propyl magnesium chloride (2.2 mL, 2.0M solution in THF, 4.4 mmol) at 0°C. The mixture was stirred at r.t. overnight, diluted with brine (50 mL) and extracted with EtOAc (50 mL). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Purification via a combiflash system then afforded the title compound (0.33 g, 71%): LCMS (ES) *m/z* 318 (M+H)<sup>+</sup>.

20 36e) Preparation of 6-butyryl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-9-carboxylic acid *tert*-butyl ester

The title compound was prepared from 6-formyl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-9-carboxylic acid 9-*tert*-butyl ester by following the procedures in Example 36c (91%): LCMS (ES) *m/z* 316 (M+H)<sup>+</sup>.

25 36f) Preparation of 1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl)-butan-1-one

The title compound was prepared from 6-butyryl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-9-carboxylic acid *tert*-butyl ester by following the procedure in Example 23b (63% yield): LCMS (ES) *m/z* 431 (2M+H)<sup>+</sup>.

30 36g) Preparation of {trans-4-[2-(6-butyryl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-carbamic acid *tert*-butyl ester

The title compound was prepared from 1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl)-butan-1-one by following the procedures in Example 23c (57% yield): LCMS (ES) *m/z* 441 (M+H)<sup>+</sup>.

35 36h) Preparation of 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-butan-1-one

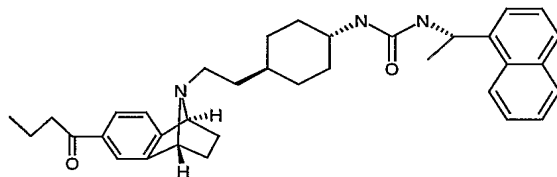
The title compound was prepared from {trans-4-[2-(6-butyryl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl}-carbamic acid *tert*-butyl ester by following the procedures in Example 23b (98% yield): LCMS (ES)  $m/z$  341 (M+H)<sup>+</sup>.

- 5 36l) Preparation of methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-butyryl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-butan-1-one and 2-methyl-quinoline-5-carboxylic acid by following the procedures in Example 19 (53% yield):

- 10 LCMS (ES)  $m/z$  510 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.09 (m, 4H), 1.27 (m, 4H), 1.60 (m, 4H), 1.76 (m, 2H), 1.83 (m, 2H), 2.10 (m, 2H), 2.70 (m, 2H), 2.78 (m, 2H), 2.99 (m, 2H), 3.06 (s, 3H), 4.0 (m, 1H), 5.12 (s, 2H), 6.49 (d, 1H), 7.57 (d, 1H), 7.69 (d, 1H), 7.94 (m, 2H), 8.07 (m, 2H), 8.53 (d, 1H), 9.36 (d, 1H).

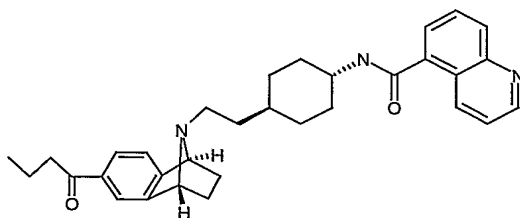
### 15 Example 37



1-(trans-4-{2-[6-Butyryl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-3-((S)-1-naphthalen-1-yl-ethyl)-urea

- The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-butan-1-one and 1-((S)-1-isocyanato-ethyl)-naphthalene by following the procedure in Example 17 (63% yield): LCMS (ES)  $m/z$  538 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  0.65 (m, 1H), 0.85 (m, 3H), 1.06 (m, 4H), 1.28 (m, 2H), 1.48 (m, 2H), 1.59 (m, 4H), 1.71 (m, 3H), 1.81 (m, 3H), 2.03 (m, 1H), 2.65 (d, 3H), 2.97 (m, 2H), 3.25 (m, 1H), 5.03 (s, 2H), 5.40 (m, 1H), 7.56 (m, 5H), 7.84 (m, 1H), 7.91 (m, 1H), 8.06 (m, 3H).

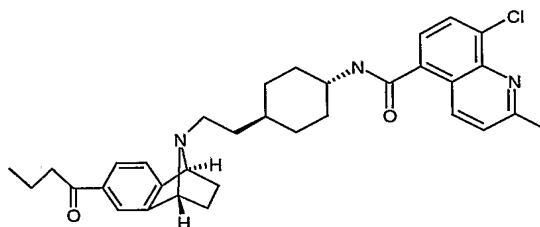
### Example 38



Quinoline-5-carboxylic acid (trans-4-{2-[6-butyryl-propanoyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-butan-1-one and quinoline-5-carboxylic acid by following the procedures in Example 19 (34% yield): LCMS (ES)  $m/z$  496 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.11 (m, 2H), 1.31 (m, 6H), 1.60 (m, 4H), 1.78 (m, 4H), 2.16 (m, 2H), 2.81 (m, 4H), 2.99 (t, 2H), 3.99 (m, 1H), 5.12 (s, 2H), 6.18 (d, 1H), 7.57 (m, 1H), 7.94 (m, 2H), 8.00 (m, 1H), 8.07 (m, 2H), 8.61 (d, 1H), 9.25 (d, 1H), 9.44 (d, 1H).

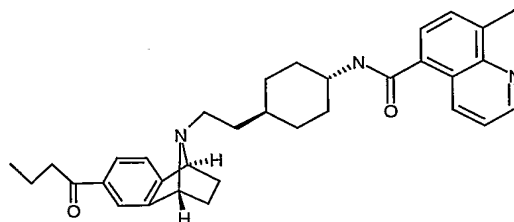
**Example 39**



8-Chloro-2-methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-butyryl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-butan-1-one and quinoline-8-chloro-2-methyl-5-carboxylic acid by following the procedures in Example 19 (34% yield): LCMS (ES)  $m/z$  544 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.10 (m, 4H), 1.22 (m, 4H), 1.61 (m, 4H), 1.73 (m, 2H), 1.85 (m, 2H), 2.14 (m, 2H), 2.76 (m, 4H), 2.85 (s, 3H), 2.99 (t, 2H), 3.95 (m, 1H), 5.09 (s, 2H), 5.90 (d, 1H), 7.44 (d, 1H), 7.50 (d, 1H), 7.56 (d, 1H), 7.78 (d, 1H), 8.07 (m, 2H), 8.66 (d, 1H).

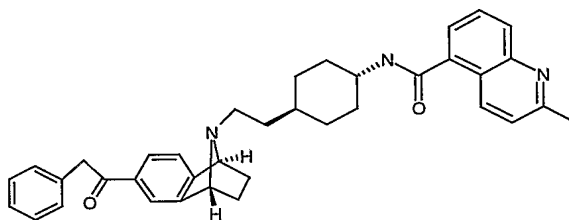
**Example 40**



8-Methyl-quinoline-5-carboxylic acid (4-{2-[6-butyryl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-butan-1-one and quinoline-8-methyl-5-carboxylic acid by following the procedures in Example 19 (87% yield): LCMS (ES)  $m/z$  510 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.12 (m, 4H), 1.27 (m, 4H), 1.59 (m, 4H), 1.75 (m, 2H), 1.83 (m, 2H), 2.12 (m, 2H), 2.70 (m, 2H), 2.79 (m, 2H), 2.94 (s, 3H), 3.01 (t, 2H), 3.97 (m, 1H), 5.12 (s, 2H), 6.22 (d, 1H), 7.55 (d, 1H), 7.77 (m, 2H), 7.87 (m, 1H), 8.07 (m, 2H), 9.39 (t, 2H).

#### Example 41



2-Methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

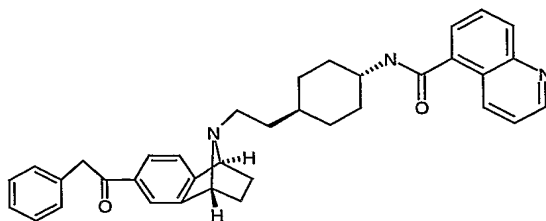
41a) Preparation of 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-phenyl-ethanone

The title compound was prepared from 6-formyl-1,2,3,4-tetrahydro-1,4-epiazano-naphthalene-9-carboxylic acid *tert*-butyl ester and PhCH<sub>2</sub>MgBr by following the procedures in 36d, 36e, 36f, 36g and 36h: LCMS (ES)  $m/z$  389 (M+H)<sup>+</sup>.

41b) Preparation of 2-methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-phenyl-ethanone and quinoline-2-methyl-5-carboxylic acid by following the procedures in Example 19 (75% yield): LCMS (ES)  $m/z$  558 (M+H)<sup>+</sup>, <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.07 (m, 1H), 1.27 (m, 4H), 1.57 (m, 4H), 1.69 (m, 2H), 2.08 (m, 2H), 2.70 (m, 2H), 2.77 (m, 2H), 3.04 (s, 3H), 3.95 (m, 1H), 4.32 (s, 2H), 5.11 (s, 2H), 6.70 (d, 1H), 7.28 (m, 3H), 7.39 (m, 2H), 7.54 (d, 1H), 7.67 (d, 1H), 7.89 (m, 2H), 8.12 (m, 2H), 8.48 (m, 1H), 9.32 (d, 1H).

#### Example 42

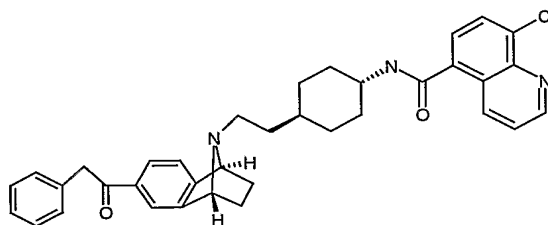


Quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-phenyl-ethanone and quinoline-5-carboxylic acid by following the procedures in Example 19 (83% yield):

LCMS (ES)  $m/z$  544 ( $M+H$ )<sup>+</sup>, <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.07 (m, 1H), 1.27 (m, 4H), 1.57 (m, 4H), 1.73 (m, 2H), 2.11 (m, 2H), 2.70 (m, 2H), 2.77 (m, 2H), 3.96 (m, 1H), 4.32 (s, 2H), 5.12 (s, 2H), 6.48 (d, 1H), 7.30 (m, 3H), 7.39 (m, 2H), 7.55 (d, 1H), 7.93 (m, 3H), 8.13 (m, 2H), 8.54 (d, 1H), 9.21 (d, 1H), 9.42 (d, 1H).

#### Example 43

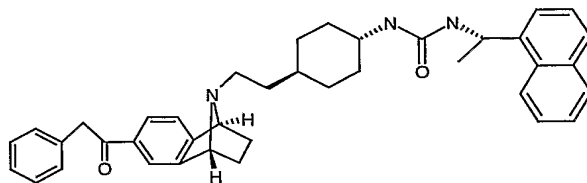


8-Chloro-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-phenyl-ethanone and quinoline-8-chloro-carboxylic acid by following the procedures in Example 19 (81% yield):

LCMS (ES)  $m/z$  578 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.07 (m, 1H), 1.24 (m, 4H), 1.57 (m, 4H), 1.71 (m, 2H), 2.13 (m, 2H), 2.67 (m, 2H), 2.77 (m, 2H), 3.96 (m, 1H), 4.32 (s, 2H), 5.13 (s, 2H), 6.20 (d, 1H), 7.34 (m, 3H), 7.39 (m, 2H), 7.61 (m, 3H), 7.81 (d, 1H), 8.12 (m, 2H), 8.86 (d, 1H), 9.14 (d, 1H).

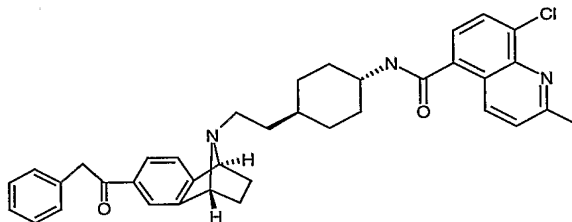
#### Example 44



1-((S)-1-Naphthalen-1-yl-ethyl)-3-(trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-urea

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-phenyl-ethanone and 1-((S)-1-isocyanato-ethyl)-naphthalene by following the procedure in Example 17 (28% yield): LCMS (ES)  $m/z$  586 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  0.65 (m, 1H), 0.9 (m, 3H), 1.05 (m, 1H), 1.28 (m, 1H), 1.52 (m, 7H), 1.69 (d, 3H), 1.87 (m, 1H), 2.64 (m, 2H), 2.71 (m, 2H), 3.26 (m, 1H), 4.30 (s, 2H), 5.04 (s, 2H), 5.42 (d, 1H), 7.32 (m, 4H), 7.39 (m, 1H), 7.56 (m, 5H), 7.82 (d, 1H), 7.91 (d, 1H), 8.07 (m, 3H).

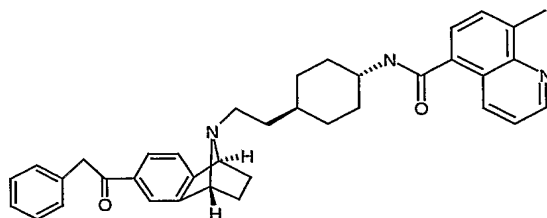
#### Example 45



8-Chloro-2-methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-phenyl-ethanone and quinoline-8-chloro-2-methyl-5-carboxylic acid by following the procedures in Example 19 (26% yield): LCMS (ES)  $m/z$  592 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.08 (m, 1H), 1.27 (m, 4H), 1.57 (m, 4H), 1.69 (m, 2H), 2.11 (m, 2H), 2.76 (m, 4H), 2.90 (s, 3H), 3.96 (m, 1H), 4.32 (s, 2H), 5.12 (s, 2H), 6.03 (d, 1H), 7.33 (m, 3H), 7.40 (m, 2H), 7.50 (d, 1H), 7.56 (m, 2H), 7.81 (d, 1H), 8.13 (m, 2H), 8.78 (d, 1H).

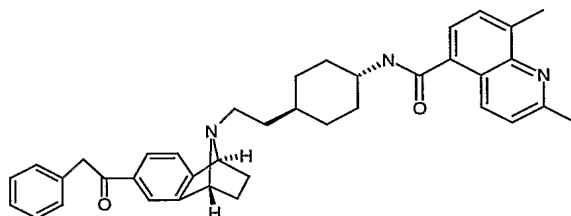
#### Example 46



**8-Methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide**

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-phenyl-ethanone and quinoline-8-methyl-5-carboxylic acid by following the procedures in Example 19 (93% yield): LCMS (ES)  $m/z$  558 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.05 (m, 1H), 1.23 (m, 4H), 1.56 (m, 4H), 1.73 (m, 2H), 2.11 (m, 2H), 2.71 (m, 2H), 2.77 (m, 2H), 2.94 (s, 3H), 3.96 (m, 1H), 4.32 (s, 2H), 5.12 (s, 2H), 6.31 (d, 1H), 7.33 (m, 3H), 7.40 (m, 2H), 7.55 (d, 1H), 7.80 (m, 2H), 7.89 (m, 1H), 8.13 (m, 2H), 9.40 (d, 1H), 9.43 (d, 1H).

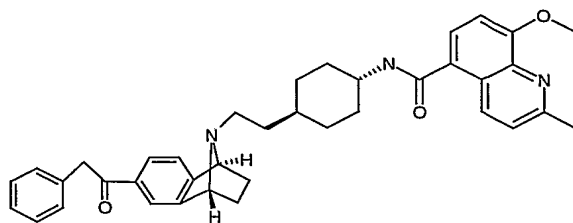
**Example 47**



**2,8-Dimethyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide**

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-phenyl-ethanone and quinoline-2,8-dimethyl-5-carboxylic acid by following the procedures in Example 19 (59% yield): LCMS (ES)  $m/z$  572 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.05 (m, 1H), 1.23 (m, 4H), 1.57 (m, 4H), 1.73 (m, 2H), 2.10 (m, 2H), 2.73 (m, 4H), 2.93 (s, 3H), 3.08 (s, 3H), 3.94 (m, 1H), 4.32 (s, 2H), 5.00 (s, 2H), 6.28 (d, 1H), 7.30 (m, 3H), 7.38 (m, 2H), 7.55 (d, 1H), 7.65 (d, 1H), 7.74 (m, 2H), 8.10 (m, 2H), 9.32 (d, 1H).

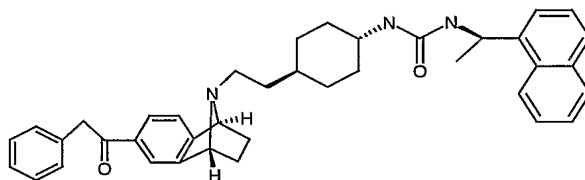
**Example 48**



8-Methoxy-2-methyl-quinoline-5-carboxylic acid (trans-4-{2-[6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-phenyl-ethanone and 8-methoxy-2-methyl-quinoline-5-carboxylic acid by following the procedures in Example 19 (33% yield): LCMS (ES)  $m/z$  588 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  1.11 (m, 1H), 1.23 (m, 4H), 1.57 (m, 4H), 1.73 (m, 2H), 2.10 (m, 2H), 2.75 (m, 4H), 3.10 (s, 3H), 3.94 (m, 1H), 4.12 (s, 3H), 4.33 (s, 2H), 5.09 (s, 2H), 6.19 (d, 1H), 7.19 (m, 31H), 7.31 (m, 3H), 7.40 (m, 2H), 7.54 (d, 1H), 7.68 (d, 1H), 7.82 (d, 1H), 8.12 (m, 2H), 9.40 (d, 1H).

**Example 49**

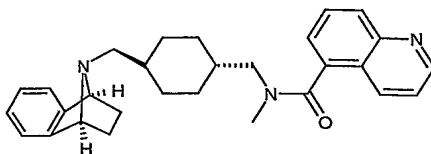


1-((R)-1-Naphthalen-1-yl-ethyl)-3-(4-{2-[(1S,4R)-6-(2-phenyl-ethanoyl)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-ethyl}-cyclohexyl)-urea

The title compound was prepared from 1-{9-[2-(trans-4-amino-cyclohexyl)-ethyl]-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl}-2-phenyl-ethanone and 1-((R)-1-isocyanato-ethyl)-naphthalene by following the procedures in Example 17 (51% yield): LCMS (ES)  $m/z$  586 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  0.65 (m, 1H), 0.85 (m, 3H), 1.05 (m, 1H), 1.28 (m, 1H), 1.51 (m, 7H), 1.68 (d, 3H), 1.86 (m, 1H), 2.66 (m, 4H), 3.27 (m, 1H), 4.30 (s, 2H), 4.98 (s, 2H), 5.42 (d, 1H), 7.32 (m, 4H), 7.39 (m, 1H), 7.56 (m, 5H), 7.83 (d, 1H), 7.91 (d, 1H), 8.01 (m, 1H), 8.07 (m, 2H).

**Example 50**





Quinoline-5-carboxylic acid methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide

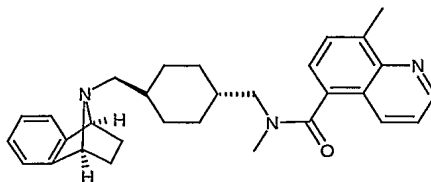
51a) Preparation of methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amine

To a solution of [trans-4-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl-methanoyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester (0.20 g, 0.52 mmol) in THF (2.0 mL), lithium aluminumhydride (1.0 N in THF, 1.56 mL, 1.56 mmol) was added. The solution was heated with a microwave reactor at 100°C for 60 minutes before it was mixed with saturated aqueous Na<sub>2</sub>SO<sub>4</sub> solution. The resultant mixture was filtered through celite. The organic phases were collected, dried over NaOH, filtered and concentrated to afford the title compound (0.11 g, 77%); LCMS (ES) *m/z* 285 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.91 (m, 4H), 1.19 (m, 2H), 1.29 (m, 1H), 1.45 (m, 2H), 1.79 (m, 4H), 1.95 (d, 2H), 2.10 (m, 2H), 2.44 (m, 5H), 4.15 (s, 2H), 7.14 (m, 2H), 7.21 (m, 2H).

51b) Preparation of quinoline-5-carboxylic acid methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide

The title compound was prepared from methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amine and quinoline-5-carboxylic acid by following the experimental procedure in Example 12d (92% yield): LCMS (ES) *m/z* 440 (M+H)<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ 0.89 (m, 1H), 1.03 (m, 1H), 1.20 (m, 1H), 1.38 (m, 1H), 1.62 (m, 5H), 1.87 (m, 3H), 2.61 (m, 2H), 2.71 (m, 2H), 2.88 (s, 2H), 3.05 (m, 1H), 3.22 (s, 1H), 3.57 (m, 1H), 4.95 (s, 1H), 5.07 (s, 1H), 7.37 (s, 2H), 7.45 (s, 2H), 7.74 (m, 1H), 7.92 (m, 1H), 8.06 (m, 1H), 8.56 (m, 1H), 8.78 (m, 1H), 9.30 (m, 1H).

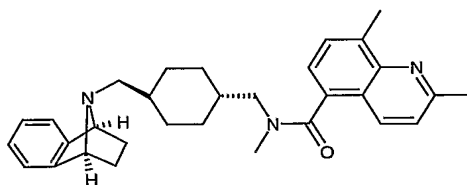
**Example 51**



8-Methyl-quinoline-5-carboxylic acid methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide

The title compound was prepared from methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amine and 8-methyl-5-quinolinecarboxylic acid by following the experimental procedure in Example 12d (93% yield): LCMS (ES)  $m/z$  454 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  0.89 (m, 1H), 1.03 (m, 1H), 1.20 (m, 1H), 1.38 (m, 1H), 1.62 (m, 5H), 1.87 (m, 3H), 2.61 (m, 2H), 2.69 (m, 2H), 2.88 (s, 2H), 2.99 (s, 3H), 3.05 (m, 1H), 3.22 (s, 1H), 3.56 (m, 1H), 4.96 (s, 1H), 5.08 (s, 1H), 7.36 (s, 2H), 7.45 (s, 2H), 7.66 (m, 1H), 7.88 (m, 1H), 7.95 (m, 1H), 8.47 (m, 1H), 9.30 (m, 1H).

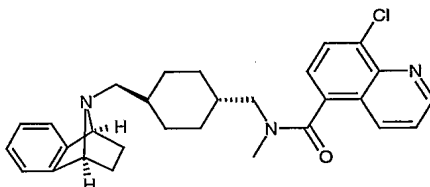
**Example 52**



2,8-Dimethyl-quinoline-5-carboxylic acid methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide

The title compound was prepared from methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amine and 2,8-dimethyl-5-quinolinecarboxylic acid by following the experimental procedure in Example 12d (74% yield): LCMS (ES)  $m/z$  468 ( $M+H$ )<sup>+</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  0.88 (m, 1H), 1.02 (m, 1H), 1.19 (m, 1H), 1.38 (m, 1H), 1.61 (m, 5H), 1.85 (m, 3H), 2.59 (m, 2H), 2.68 (m, 2H), 2.86 (s, 1H), 2.95 (s, 3H), 3.13 (s, 3H), 3.07 (m, 1H), 3.20 (s, 2H), 3.55 (m, 1H), 4.95 (s, 1H), 5.08 (s, 1H), 7.38 (m, 2H), 7.45 (s, 2H), 7.62 (m, 1H), 7.76 (m, 1H), 7.86 (m, 1H), 8.77 (m, 1H).

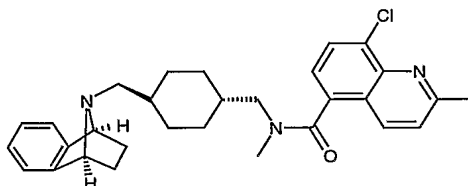
**Example 53**



8-Chloro-quinoline-5-carboxylic acid methyl-{4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide

The title compound was prepared from methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amine and 8-chloro-5-quinolinecarboxylic acid by following the experimental procedure in Example 12d (90% yield): LCMS (ES)  $m/z$  474 ( $M^+$ );  $^1H$ -NMR( $CDCl_3$ )  $\delta$  0.89 (m, 1H), 1.02 (m, 1H), 1.19 (m, 1H), 1.38 (m, 1H), 1.61 (m, 5H), 1.86 (m, 3H), 2.60 (m, 2H), 2.69 (m, 2H), 2.86 (s, 2H), 3.01 (m, 1H), 3.23 (s, 1H), 3.56 (m, 1H), 4.99 (s, 1H), 5.10 (s, 1H), 7.38 (s, 2H), 7.42 (s, 2H), 7.49 (m, 1H), 7.71 (m, 1H), 7.96 (m, 1H), 8.38 (m, 1H), 9.23 (m, 1H).

## 10 Example 54

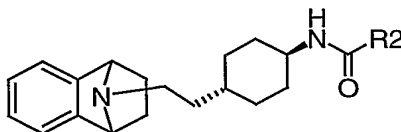


8-Chloro-2-methyl-quinoline-5-carboxylic acid methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amide

The title compound was prepared from methyl-{trans-4-[1-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)methyl]-cyclohexylmethyl}-amine and 8-chloro-2-methyl-5-quinolinecarboxylic acid by following the experimental procedure in Example 12d (97% yield): LCMS (ES)  $m/z$  488( $M^+$ );  $^1H$ -NMR( $CDCl_3$ )  $\delta$  0.87 (m, 1H), 1.01 (m, 1H), 1.18 (m, 1H), 1.38 (m, 1H), 1.61 (m, 5H), 1.85 (m, 3H), 2.59 (m, 2H), 2.68 (m, 2H), 2.86 (s, 1H), 3.02 (s, 3H), 3.08(m, 1H), 3.22 (s, 2H), 3.55 (m, 1H), 4.97 (s, 1H), 5.09 (s, 1H), 7.38 (m, 2H), 7.46 (s, 2H), 7.53 (m, 1H), 7.68 (m, 1H), 7.99 (m, 1H), 8.47 (m, 1H).

In addition, following either the procedure for the preparation of Example 17 (ureas) or for the preparation of Example 12 (amides), the following compounds (Eaxamples 56-136) were synthesized and tested:

**Table 1:**



| Example | Compound Name   | LC/MS (ES)<br>(M+H) <sup>+</sup> |
|---------|---|----------------------------------|
| 55      | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2-(4-pyridinyl)acetamide                 | 390.0                            |
| 56      | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2-pyridinylmethyl)urea                | 405.0                            |
| 57      | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(cyclohexylmethyl)urea                 | 410.0                            |
| 58      | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(4-hydroxycyclohexyl)urea              | 412.0                            |
| 59      | N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-methyl-N-(phenylmethyl)urea           | 418.0                            |
| 60      | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[2-(2-pyridinyl)ethyl]urea             | 419.0                            |
| 61      | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[(2-hydroxyphenyl)methyl]urea          | 420.0                            |
| 62      | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]urea | 421.0                            |
| 63      | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[(4-fluorophenyl)methyl]urea           | 422.0                            |
| 64      | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2-(2-pyrimidinylthio)acetamide           | 423.0                            |
| 65      | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-                                       | 426.0                            |

|           |  |       |
|-----------|--|-------|
|           | quinolinecarboxamide   |       |
| <b>66</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-1-methyl-1H-indole-2-carboxamide                    | 428.0 |
| <b>67</b> | (2E)-N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-4-oxo-4-phenyl-2-butenamide                    | 429.0 |
| <b>68</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2,3-dihydro-1H-inden-1-yl)urea                   | 430.0 |
| <b>69</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(3-phenylpropyl)urea                              | 432.0 |
| <b>70</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[(4-chlorophenyl)methyl]urea                      | 439.0 |
| <b>71</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1,1a,6,6a-tetrahydrocyclopropa[a]inden-1-yl)urea | 442.0 |
| <b>72</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1H-indol-3-ylmethyl)urea                         | 443.0 |
| <b>73</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1H-benzimidazol-2-ylmethyl)urea                  | 444.0 |
| <b>74</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1,2,3,4-tetrahydro-2-naphthalenyl)urea           | 444.0 |
| <b>75</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1,2,3,4-tetrahydro-1-naphthalenyl)urea           | 444.0 |
| <b>76</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N,N-dimethylphenylalaninamide                       | 446.0 |

|           |   |       |
|-----------|---|-------|
| <b>77</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(4-phenylbutyl)urea                              | 446.0 |
| <b>78</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2-methyl-1,2,3,4-tetrahydro-2-naphthalenyl)urea | 458.0 |
| <b>79</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-4-(2-pyridinyl)-1-piperazinecarboxamide            | 460.0 |
| <b>80</b> | N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-(3-hydroxypropyl)-N-(phenylmethyl)urea          | 462.0 |
| <b>81</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[2-(4-pyridinyl)ethyl]urea formate               | 419.0 |
| <b>82</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2,2-diphenylacetamide                              | 465.0 |
| <b>83</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[3-(1H-imidazol-1-yl)propyl]urea formate         | 422.0 |
| <b>84</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[[4-(trifluoromethyl)phenyl]methyl]urea          | 472.0 |
| <b>85</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-4-(phenylmethyl)-1-piperazinecarboxamide           | 473.0 |
| <b>86</b> | N-{5-[(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)amino]-5-oxopentyl}benzamide                    | 474.0 |
| <b>87</b> | 1,1-dimethylethyl 2-[[[(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)amino]carbonyl]benzoate        | 475.0 |
| <b>88</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-   | 479.0 |

|    |  |       |
|----|--|-------|
|    | naphthalen-9-yl)-ethyl]-cyclohexyl)-2,2-diphenylpropanamide  |       |
| 89 | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3,3-diphenylpropanamide                         | 479.0 |
| 90 | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1H-indol-3-ylmethyl)urea formate             | 443.0 |
| 91 | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[[3-(dimethylamino)phenyl]methyl]urea formate | 447.0 |
| 92 | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(4-methylphenyl)-3-phenylpropanamide          | 493.0 |
| 93 | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-4,4-diphenylbutanamide                          | 493.0 |
| 94 | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-4-[(phenylcarbonyl)amino]benzamide              | 494.0 |
| 95 | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1,2-diphenylethyl)urea                       | 494.0 |
| 96 | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2,2-diphenylethyl)urea                       | 494.0 |
| 97 | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2,2-diphenylethyl)urea                       | 494.0 |
| 98 | N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N,1-bis(phenylmethyl)urea                      | 494.0 |
| 99 | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2-  | 495.0 |

|            |  |       |
|------------|--|-------|
|            | (methyloxy)-2,2-diphenylacetamide  |       |
| <b>100</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1-naphthalenylmethyl)urea formate                        | 454.0 |
| <b>101</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(3,3-diphenylpropyl)urea                                  | 508.0 |
| <b>102</b> | N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-1-(2-phenylethyl)-1-(phenylmethyl)urea                     | 508.0 |
| <b>103</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2-hydroxy-2,2-diphenylethyl)urea                         | 510.0 |
| <b>104</b> | N-[2-({[(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)amino]carbonyl}amino)ethyl]-4-methylbenzenesulfonamide | 511.0 |
| <b>105</b> | 1,1-dimethylethyl N-{{[(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)amino]carbonyl}-L-phenylalaninate       | 518.0 |
| <b>106</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-4-(phenylmethyl)-1-piperazinecarboxamide formate            | 473.0 |
| <b>107</b> | N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-(3,3-diphenylpropyl)-N-methylurea                        | 522.0 |
| <b>108</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2-{3-[hydroxy(3-pyridinyl)methyl]phenyl}ethyl)urea       | 525.0 |
| <b>109</b> | 3-[[{[(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)amino]carbonyl}amino)methyl]benzenesulfonamide formate   | 483.0 |



|            |   |       |
|------------|---|-------|
| <b>110</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[1-(phenylmethyl)-4-piperidinyl]urea formate                       | 360.0 |
| <b>111</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(3-phenylpropyl)urea trifluoroacetate                              | 432.0 |
| <b>112</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[5,8-bis(methyloxy)-1,2,3,4-tetrahydro-2-naphthalenyl]urea formate | 504.0 |
| <b>113</b> | N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-(3,3-diphenylpropyl)-N-propylurea                                 | 550.0 |
| <b>114</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(3,3-diphenylpropyl)urea formate                                   | 508.0 |
| <b>115</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1-methyl-2,2-diphenylethyl)urea formate                           | 508.0 |
| <b>116</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2-[(2-methylphenyl)(phenyl)methyl]benzamide                          | 555.0 |
| <b>117</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2-hydroxy-1,1-diphenylethyl)urea formate                          | 510.0 |
| <b>118</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-4-(diethylamino)-2,2-diphenylbutanamide                              | 564.0 |
| <b>119</b> | N,N'-bis(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)urea  | 567.0 |
| <b>120</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(3-hydroxy-3,3-diphenylpropyl)urea formate                         | 524.0 |

|            |   |       |
|------------|---|-------|
| <b>121</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[(1S)-2-hydroxy-1-methyl-2,2-diphenylethyl]urea formate        | 524.0 |
| <b>122</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(2-{3-[hydroxy(3-pyridinyl)methyl]phenyl}ethyl)urea formate    | 525.0 |
| <b>123</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-(1,1-dimethyl-3,3-diphenylpropyl)urea formate                  | 536.0 |
| <b>124</b> | N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-(3,3-diphenylpropyl)-N-ethylurea formate                      | 536.0 |
| <b>125</b> | N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-methyl-N-(2,2,2-triphenylethyl)urea                           | 584.0 |
| <b>126</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-phenyl-3-{3-[(phenylmethyl)oxy]phenyl}propanamide              | 585.0 |
| <b>127</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2-hydroxy-2,2-diphenylacetamide trifluoroacetate (salt)          | 481.0 |
| <b>128</b> | N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-ethyl-N-(3-hydroxy-3,3-diphenylpropyl)urea formate            | 552.0 |
| <b>129</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2-{bis[4-(dimethylamino)phenyl]methyl}benzamide                  | 314.0 |
| <b>130</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[4-(dimethylamino)phenyl]-3-phenylpropanamide trifluoroacetate | 522.0 |
| <b>131</b> | N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-  | 598.0 |

|            |  |       |
|------------|--|-------|
|            | naphthalen-9-yl)-ethyl]-cyclohexyl)-N-(3,3-diphenylpropyl)-N-(phenylmethyl)urea formate  |       |
| <b>132</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-2,2-bis(4-chlorophenyl)acetamide trifluoroacetate                 | 533.0 |
| <b>133</b> | N-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-4-(diethylamino)-2,2-diphenylbutanamide trifluoroacetate          | 564.0 |
| <b>134</b> | 1-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-3-[3-(4-biphenyl)-3-(4-chlorophenyl)-3-hydroxypropyl]urea formate | 634.0 |
| <b>135</b> | N'-(trans-4-[2-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl)-ethyl]-cyclohexyl)-N-(2,2-diphenylethyl)-N-(phenylmethyl)urea trifluoroacetate      | 584.0 |

### **BIOLOGICAL EXAMPLES**

The inhibitory effects of compounds at the M<sub>3</sub> mAChR of the present invention are  
5 determined by the following *in vitro* and *in vivo* functional assays:

#### **Analysis of Inhibition of Receptor Activation by Calcium Mobilization:**

Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described (Sarau,  
10 H. M., R. S. Ames, J. Chambers, C. Ellis, N. Elshourbagy, J. J. Foley, D. B. Schmidt, R. M. Muccitelli, O. Jenkins, P. R. Murdock, N. C. Herrity, W. Halsey, G. Sathe, A. I. Muir, P. Nuthulaganti, G. M. Dytko, P. T. Buckley, S. Wilson, D. J. Bergsma, and D. W. Hay. 1999. Identification, molecular cloning, expression, and characterization of a cysteinyl leukotriene receptor. Mol Pharmacol 56:657-663).  
15 CHO cells stably expressing M<sub>3</sub> mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 µl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO),

and 4  $\mu\text{M}$  Fluo-3-acetoxymethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10 minutes at 37° C. Cells were then washed 3 times and

5 incubated for 10 minutes at 37° C in 100  $\mu\text{l}$  of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM  $\text{KH}_2\text{PO}_4$ , 25 mM NaH  $\text{CO}_3$ , 1.0 mM  $\text{CaCl}_2$ , 1.1 mM  $\text{MgCl}_2$ , 11 mM glucose, 20mM HEPES (pH 7.4)). 50  $\mu\text{l}$  of compound ( $1 \times 10^{-11}$  –  $1 \times 10^{-5}$  M final in the assay) was added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader

10 (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50  $\mu\text{l}$  of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50  $\mu\text{l}/\text{sec}$ . Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change

15 in emission intensity is directly related to cytosolic calcium levels (Sullivan, E., E. M. Tucker, and I. L. Dale. 1999. Measurement of  $[\text{Ca}^{2+}]$  using the Fluorometric Imaging Plate Reader (FLIPR). *Methods Mol Biol* 114:125-133). The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and

20 analyzed using GraphPad PRISM software.

### **Methacholine-induced bronchoconstriction**

Airway responsiveness to methacholine was determined in awake, unrestrained BalbC mice ( $n = 6$  each group). Barometric plethysmography was

25 used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine (Hamelmann, E., J. SCHWARZE, K. TAKEDA, A. OSHIBA, G. á. LARSEN, C. á. IRVIN, and E. á. GELFAND. 1997. Noninvasive Measurement of Airway Responsiveness in Allergic Mice Using Barometric

30 Plethysmography. *Am.J.Respir.Crit.Care Med.* 156:766-775). Mice were pretreated with 50  $\mu\text{l}$  of compound (0.003-10  $\mu\text{g}/\text{mouse}$ ) in 50  $\mu\text{l}$  of vehicle (10% DMSO) intranasally, i.v., i.p. or p.o, and were then placed in the plethysmography chamber. Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an

aerosol of methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software.

5           The present compounds are useful for treating a variety of indications, including but not limited to respiratory-tract disorders such as chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema, and allergic rhinitis; gastrointestinal-tract disorders such as irritable bowel syndrome, spasmodic colitis, gastroduodenal ulcers,  
10   gastrointestinal convulsions or hyperanakisia, diverticulitis, pain accompanying spasms of gastrointestinal smooth musculature; urinary-tract disorders accompanying micturition disorders including neurogenic pollakisuria, neurogenic bladder, nocturnal enuresis, psychosomatic bladder, incontinence associated with bladder spasms or chronic cystitis, urinary urgency or pollakiuria, and motion  
15   sickness.

Methods of administering the present compounds will be readily apparent to the skilled artisan.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or  
20   blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20µg-10mg of the compound of formula (I) optionally in combination with  
25   another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients.

Suitably, the medicament dispenser is of a type selected from the group consisting of a reservoir dry powder inhaler (RDPI), a multi-dose dry powder inhaler (MDPI), and a metered dose inhaler (MDI).

30           By reservoir dry powder inhaler (RDPI) it is meant an inhaler having a reservoir form pack suitable for comprising multiple (un-metered doses) of medicament in dry powder form and including means for metering medicament dose from the reservoir to a delivery position. The metering means may for example comprise a metering cup, which is movable from a first position where the cup may

be filled with medicament from the reservoir to a second position where the metered medicament dose is made available to the patient for inhalation.

By multi-dose dry powder inhaler (MDPI) is meant an inhaler suitable for dispensing medicament in dry powder form, wherein the medicament is comprised within a multi-dose pack containing (or otherwise carrying) multiple, define doses (or parts thereof) of medicament. In a preferred aspect, the carrier has a blister pack form, but it could also, for example, comprise a capsule-based pack form or a carrier onto which medicament has been applied by any suitable process including printing, painting and vacuum occlusion.

The formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

In one aspect, the multi-dose pack is a blister pack comprising multiple blisters for containment of medicament in dry powder form. The blisters are typically arranged in regular fashion for ease of release of medicament therefrom.

In one aspect, the multi-dose blister pack comprises plural blisters arranged in generally circular fashion on a disc-form blister pack. In another aspect, the multi-dose blister pack is elongate in form, for example comprising a strip or a tape.

Preferably, the multi-dose blister pack is defined between two members peelably secured to one another. US Patents Nos. 5,860,419, 5,873,360 and 5,590,645 describe medicament packs of this general type. In this aspect, the device is usually provided with an opening station comprising peeling means for peeling the members apart to access each medicament dose. Suitably, the device is adapted for use where the peelable members are elongate sheets which define a

plurality of medicament containers spaced along the length thereof, the device being provided with indexing means for indexing each container in turn. More preferably, the device is adapted for use where one of the sheets is a base sheet having a plurality of pockets therein, and the other of the sheets is a lid sheet, each  
5 pocket and the adjacent part of the lid sheet defining a respective one of the containers, the device comprising driving means for pulling the lid sheet and base sheet apart at the opening station.

By metered dose inhaler (MDI) it is meant a medicament dispenser suitable for dispensing medicament in aerosol form, wherein the medicament is comprised  
10 in an aerosol container suitable for containing a propellant-based aerosol medicament formulation. The aerosol container is typically provided with a metering valve, for example a slide valve, for release of the aerosol form medicament formulation to the patient. The aerosol container is generally designed to deliver a predetermined dose of medicament upon each actuation by means of the valve,  
15 which can be opened either by depressing the valve while the container is held stationary or by depressing the container while the valve is held stationary.

Where the medicament container is an aerosol container, the valve typically comprises a valve body having an inlet port through which a medicament aerosol formulation may enter said valve body, an outlet port through which the aerosol  
20 may exit the valve body and an open/close mechanism by means of which flow through said outlet port is controllable.

The valve may be a slide valve wherein the open/close mechanism comprises a sealing ring and receivable by the sealing ring a valve stem having a dispensing passage, the valve stem being slidably movable within the ring from a  
25 valve-closed to a valve-open position in which the interior of the valve body is in communication with the exterior of the valve body via the dispensing passage.

Typically, the valve is a metering valve. The metering volumes are typically from 10 to 100  $\mu\text{l}$ , such as 25  $\mu\text{l}$ , 50  $\mu\text{l}$  or 63  $\mu\text{l}$ . Suitably, the valve body defines a metering chamber for metering an amount of medicament formulation and an  
30 open/close mechanism by means of which the flow through the inlet port to the metering chamber is controllable. Preferably, the valve body has a sampling chamber in communication with the metering chamber via a second inlet port, said inlet port being controllable by means of an open/close mechanism thereby regulating the flow of medicament formulation into the metering chamber.

The valve may also comprise a 'free flow aerosol valve' having a chamber and a valve stem extending into the chamber and movable relative to the chamber between dispensing and non-dispensing positions. The valve stem has a configuration and the chamber has an internal configuration such that a metered volume is defined therebetween and such that during movement between is non-dispensing and dispensing positions the valve stem sequentially: (i) allows free flow of aerosol formulation into the chamber, (ii) defines a closed metered volume for pressurized aerosol formulation between the external surface of the valve stem and internal surface of the chamber, and (iii) moves with the closed metered volume within the chamber without decreasing the volume of the closed metered volume until the metered volume communicates with an outlet passage thereby allowing dispensing of the metered volume of pressurized aerosol formulation. A valve of this type is described in U.S. Patent No. 5,772,085. Additionally, intra-nasal delivery of the present compounds is effective.

To formulate an effective pharmaceutical nasal composition, the medicament must be delivered readily to all portions of the nasal cavities (the target tissues) where it performs its pharmacological function. Additionally, the medicament should remain in contact with the target tissues for relatively long periods of time. The longer the medicament remains in contact with the target tissues, the medicament must be capable of resisting those forces in the nasal passages that function to remove particles from the nose. Such forces, referred to as 'mucociliary clearance', are recognised as being extremely effective in removing particles from the nose in a rapid manner, for example, within 10-30 minutes from the time the particles enter the nose.

Other desired characteristics of a nasal composition are that it must not contain ingredients which cause the user discomfort, that it has satisfactory stability and shelf-life properties, and that it does not include constituents that are considered to be detrimental to the environment, for example ozone depleters.

A suitable dosing regime for the formulation of the present invention when administered to the nose would be for the patient to inhale deeply subsequent to the nasal cavity being cleared. During inhalation the formulation would be applied to one nostril while the other is manually compressed. This procedure would then be repeated for the other nostril.

A preferable means for applying the formulation of the present invention to the nasal passages is by use of a pre-compression pump. Most preferably, the pre-



compression pump will be a VP7 model manufactured by Valois SA. Such a pump is beneficial as it will ensure that the formulation is not released until a sufficient force has been applied, otherwise smaller doses may be applied. Another advantage of the pre-compression pump is that atomisation of the spray is ensured as it will not release the formulation until the threshold pressure for effectively atomising the spray has been achieved. Typically, the VP7 model may be used with a bottle capable of holding 10-50ml of a formulation. Each spray will typically deliver 50-100 $\mu$ l of such a formulation, therefore, the VP7 model is capable of providing at least 100 metered doses.

10

### **Examples of Nasal Formulations**

#### **Example 1: Nasal formulation containing active**

A formulation for intranasal delivery was prepared with ingredients as follows:

|    |                |            |
|----|----------------|------------|
|    |                | to 100%    |
| 15 | Active         | 0.1% w/w   |
|    | Polysorbate 80 | 0.025% w/w |
|    | Avicel RC591   | 1.5% w/w   |
|    | Dextrose       | 5.0% w/w   |
|    | BKC            | 0.015% w/w |
| 20 | EDTA           | 0.015% w/w |
|    | water          | to 100%    |

in a total amount suitable for 120 actuations and the formulation was filled into a bottle fitted with a metering valve adapted to dispense 50 or 100  $\mu$ l per actuation. The device was fitted into a nasal actuator (Valois).

25

#### **Example 2: Nasal formulation containing active**

A formulation for intranasal delivery was prepared with ingredients as follows:

|    |           |            |
|----|-----------|------------|
|    | Active    | 0.005% w/w |
|    | Tyloxapol | 2% w/w     |
| 30 | dextrose  | 5% w/w     |
|    | BKC       | 0.015% w/w |
|    | EDTA      | 0.015% w/w |
|    | water     | to 100%    |

in a total amount suitable for 120 actuations and the formulation was filled into a bottle (plastic or glass) fitted with a metering valve adapted to dispense 50 or 100 µl per actuation

The device was fitted into a nasal actuator (Valois, e.g. VP3, VP7 or VP7D)

5

Example 3: Nasal formulation containing active

A formulation for intranasal delivery was prepared with ingredients as follows:

|              |            |
|--------------|------------|
| active       | 0.05% w/w  |
| Triton X-100 | 5% w/w     |
| Dextrose     | 4% w/w     |
| BKC          | 0.015% w/w |
| EDTA         | 0.015% w/w |
| water        | to 100%    |

10

in a total amount suitable for 120 actuations and the formulation was filled into a bottle fitted with a metering valve adapted to dispense 50 or 100 µl per actuation.

15

Example 4: Nasal formulation containing active

A formulation for intranasal delivery was prepared with ingredients as follows:

|           |            |
|-----------|------------|
| active    | 0.05% w/w  |
| Tyloxapol | 5% w/w     |
| dextrose  | 5% w/w     |
| BKC       | 0.015% w/w |
| EDTA      | 0.015% w/w |
| water     | to 100%    |

20

in a total amount suitable for 120 actuations and the formulation was filled into a bottle fitted with a metering valve adapted to dispense 50 or 100 µl per actuation

25

The device was fitted into a nasal actuator (Valois).

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

30

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

5           The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the

10   Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

          The patents and patent applications described in this application are herein incorporated by reference.

15